INSTITUTO NACIONAL DE
CIENCIAS MÉDICAS
Y NUTRICIÓN
SALVADOR ZUBIRÁN

MÉXICO, D.F., A 24 DE MARZO DE 2014.

DRA. ANDREA HINOJOSA AZAOLA
INVESTIGADORA PRINCIPAL
DEPTO. DE INMUNOLOGÍA Y REUMATOLOGÍA
PRESENTE

Por este medio, nos permitimos informarle que el ***Comité de Investigación***, así como el ***Comité de Ética en Investigación*** del Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, **ha revisado y aprobado** el Protocolo de Investigación Clínica, titulado:

"Características clínicas, sobrevida y desenlace renal de los pacientes con vasculitis asociadas a ANCA en tratamiento con plasmaféresis"
Versión 7 de marzo, 2014.
REF. 1216

La vigencia de la aprobación termina el día 24 de marzo de 2015. Si la duración del estudio es mayor tendrá que solicitar la re-aprobación anual del mismo, informando sobre los avances y resultados parciales de su investigación e incluyendo todos los datos sobresalientes y conclusiones.

Sin más por el momento quedamos de usted.

ATENTAMENTE,

DR. CARLOS A. AGUILAR SALINAS
PRESIDENTE
COMITÉ DE INVESTIGACIÓN

26 MAR 2014

DR. ARTURO GALINDO FRAGA
PRESIDENTE
COMITÉ DE ÉTICA EN INVESTIGACIÓN

c.c.p. Dr. Rubén Lisker Y., Director de Investigación.

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INCMNSZ
26 MAR 2014
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ACUSE

CIUDAD DE MÉXICO, A 18 DE FEBRERO DE 2016

DRA. ANDREA HINOJOSA AZAOLA
INVESTIGADORA PRINCIPAL
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COL. BELISARIO DOMÍNGUEZ SECCIÓN XVI
DEL. TLALPAN, C.P. 14080, CIUDAD DE MÉXICO
PRESENTE

Le informamos que con relación al Protocolo de Investigación Clínica, titulado:

"Características clínicas, sobrevida y desenlace renal de los pacientes con vasculitis asociadas a ANCA en tratamiento con plasmaféresis"
REF. 1216

Se toma conocimiento del **cierre** de estudio detallado en su carta de fecha 4 de febrero de 2016.

Sin más otro particular, reciba un cordial saludo.

ATENTAMENTE,

DR. CARLOS A. AGUILAR SALINAS
PRESIDENTE
COMITÉ DE INVESTIGACIÓN

DR. ARTURO GALINDO FRAGA
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Salvador Zubirán

17 MAR 2014

INSTITUTO NACIONAL DE CIENCIAS MÉDICAS Y NUTRICIÓN

SALVADOR ZUBIRAN

Dirección de Investigación

FORMA ÚNICA PARA REGISTRO DE PROYECTOS

FECHA DE RECEPCIÓN: 07/03/2014 CLAVE: IRE-1216-14/15-1

TÍTULO: Características clínicas, sobrevida y desenlace renal de los pacientes con vasculitis asociadas a ANCA en tratamiento con plasmaféresis.

INVESTIGADOR RESPONSABLE: HINOJOSA AZAOLA ANDREA

DEPARTAMENTO O SERVICIO: DEPARTAMENTO DE INMUNOLOGÍA Y REUMATOLOGÍA

TIPO DE INVESTIGACIÓN: INVESTIGACIÓN CLÍNICA

PATROCINADORES:

Patrocinador	Cantidad

VIGENCIA DEL PROYECTO: Del 07/03/2014 al 06/03/2015

Trimestre 1	Trimestre 2	Trimestre 3	Trimestre 4

COSTO TOTALES DE LA INVESTIGACIÓN	
Personal	$ 0.00
(sueldos y sobresueldos al personal)	
Equipos	$ 0.00
(de laboratorio, cómputo, transporte, etc.)	
Materiales	$ 0.00
(reactivos, consumibles, desechables, etc.)	
Animales	$ 0.00
(adquisición, cuidado, procedimientos, etc.)	
Estudios	$ 0.00
(de laboratorio, gabinete,especiales,etc.)	
Viaticos	$ 0.00
(reuniones científicas y trabajo de campo)	
Publicaciones	$ 0.00
costo directos de publicación, sobregiro)	

INSTITUCIONES PARTICIPANTES

FIRMAS

Investigador responsable		Jefe de Departamento
Comité de Investigación en Humanos		Comité de Investigación en Animales
Director de Investigación		Director General

Fecha de resolución

11-ABRIL-2014

Plasmapheresis Therapy in ANCA-Associated Vasculitides: A Single-Center Retrospective Analysis of Renal Outcome and Mortality

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Background: The evidence of the benefit of plasmapheresis in renal and survival outcomes in patients with severe manifestations of ANCA-associated vasculitides is inconsistent. **Purpose:** To address whether plasmapheresis is associated with improvement in renal function and survival at 12 months in patients with severe manifestations of ANCA-associated vasculitides. **Patients and Methods:** Single-center retrospective comparative cohort of 24 patients with granulomatosis with polyangiitis or microscopic polyangiitis that received plasmapheresis adjunctive to conventional therapy (steroids and immunosuppressants), matched 1:1 according to age, estimated glomerular filtration rate (eGFR) and disease activity with 24 patients treated with standard treatment only. Comorbidities, demographic, clinical, treatment and laboratory characteristics were recorded. **Results:** After 12 months both groups showed improvement in eGFR (19.0 ± 14.34 to 41.61 ± 37.77 ml/min, $p = 0.003$ in plasmapheresis group; 23.16 ± 14.71 to 39.86 ± 25.67 ml/min, $p = 0.001$ in conventional therapy group). No differences were found between groups ($p = 0.68$). Patients free of dialysis at 12 months after intervention increased in the plasmapheresis group from 9/24 (38%) to 12/24 (50%), $p = 0.5$; and in the conventional therapy group from 19/24 (79%) to 22/24 (92%), $p = 0.25$. Difference between groups was significant at 12 months ($p = 0.001$). Survival at 12 months after intervention was 79% in the plasmapheresis group and 96% in the conventional therapy group ($p = 0.08$). The main cause of death was infectious and a tendency for a higher prevalence of severe infections was observed in patients that received plasmapheresis ($p = 0.07$). **Conclusion:** Both plasmapheresis and conventional therapy improved eGFR at 12 months after intervention. Dialysis independence and survival were similar between groups. J. Clin. Apheresis 00:000–000, 2015.

Key words: plasma exchange; ANCA; granulomatosis with polyangiitis; microscopic polyangiitis

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA) associated vasculitides (AAV) are rare, potentially fatal diseases with multiorgan involvement, characterized by the presence of vasculitis and necrosis affecting small vessels [1]. The main phenotypes of AAV are granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis) and microscopic polyangiitis (MPA); these entities share clinical features, pathophysiologic mechanisms, and therapeutic strategies [2]. Eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome), also an AAV, is characterized by allergic and vasculitic features and is usually studied separately from GPA and MPA [3].

Renal and pulmonary involvement is common in AAV, with an incidence of glomerulonephritis of 38–70% in GPA and 80-100% in MPA, and pulmonary involvement of 60-85% and 25-55%, respectively [4,5]. Rapidly progressive glomerulonephritis (RPGN) and diffuse alveolar hemorrhage (DAH) are considered severe disease manifestations that compromise organic function and may be life-threatening [2]. Patients with renal involvement show worse prognosis, since higher serum creatinine concentrations and dialysis dependence at diagnosis predict progression to end-stage renal disease (ESRD), and both high serum creatinine and ESRD are independently associated with increased mortality in these patients despite immunosuppressive therapy [6].

The traditional treatment regimen for severe disease comprises the combination of cyclophosphamide (CYC) and glucocorticoids, with initial remission rates

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of 80-90%. Plasma exchange is currently indicated as adjuvant therapy to standard treatment in patients with AAV that present severe manifestations [2,7–9]. The American Society for Apheresis (ASFA) guidelines for treating AAV assigns different categories of indication for therapeutic apheresis in patients presenting with ANCA-associated RPGN according to the disease setting (category I in dialysis dependence and DAH, and category III in dialysis independence) [8].

In the largest clinical trial performed to this day that investigated whether the addition of plasma exchange is more effective than intravenous methylprednisolone in the achievement of renal recovery in patients with AAV, 67 patients who received high-dose steroids were compared to 70 patients that received adjuvant plasmapheresis [10]. Both groups received oral CYC and prednisolone. Plasma exchange was associated with a reduction in risk for progression to ESRD at 12 months, but no differences were found in mortality and adverse events between groups. However, long-term follow-up for a median of 3.9 years showed that although short-term results of plasma exchange were encouraging, the long-term benefits remain unclear, since no differences were found between groups in either renal or mortality outcomes [11]. Smaller clinical trials have been complemented with descriptive case series and have suggested improvement in renal function and mortality associated with plasmapheresis therapy [12–15], but strong evidence of a clear benefit is lacking.

Given the poor outcomes of patients with AAV, we aimed to address whether plasma exchange is associated with improvement in renal function and survival in patients treated at our center.

PATIENTS AND METHODS

Study Design and Patients

After approval by the Institutional Review Board, we conducted a single-center retrospective comparative cohort study of patients diagnosed with AAV presenting with severe disease manifestations and treated with either conventional therapy alone or with adjuvant plasma exchange. All patients were followed at our tertiary care center in Mexico City from 2000 to 2012.

Eligible patients were 18–75 years of age and had diagnosis of GPA according to the American College of Rheumatology 1990 classification criteria [16] or Chapel Hill 2012 definition [1], or MPA according to this later definition. All patients had ANCA positivity at diagnosis (determined by either immunofluorescence or ELISA), and presented clinical manifestations such as RPGN and/or DAH.

Three hundred and eleven patients with AAV were identified in the period of observation; of them, twenty-four received plasma exchange as adjuvant therapy and fulfilled inclusion criteria. The moment when they received plasma exchange was established as time zero for this study (time of intervention). These patients were matched 1:1 with 24 patients that presented with severe disease manifestations such as renal impairment and/or DAH and received conventional therapy without plasmapheresis. Patients were matched according to the following variables: Age at diagnosis (±7 years); disease activity at the time of intervention (Birmingham Vasculitis Activity Score for Wegener's Granulomatosis, BVAS/WG range ±6) [17]; and estimated glomerular filtration rate (eGFR) calculated using the four-variable MDRD equation [18] (eGFR ±16 mL/minute) at the time of intervention. Patients were followed-up for at least one year, medical files were reviewed and clinical data was recorded. The patient selection algorithm is shown in Figure 1.

Patients with secondary forms of vasculitis (diagnosis of a different rheumatic disease, hepatitis B or C virus infection, HIV infection), diagnosis of EGPA and acute renal injury not attributable to vasculitis were excluded.

Treatment

Patients in the conventional therapy group received high-dose steroids (prednisone 1 mg/kg/d, either preceded or not by IV methylprednisolone) and one or more immunosuppressants (CYC, azathioprine, and/or rituximab), without plasmapheresis. Patients in the plasma exchange group received at least three plasmapheresis sessions as adjunctive treatment to the conventional therapy. A Rheumatologist determined the therapeutic regimen in each patient.

Assessments

Demographic data, clinical characteristics including disease activity (BVAS/WG score) and prognosis at diagnosis (Five Factor Score, FFS) [19], comorbidities present previous to AAV diagnosis, treatment information, laboratory characteristics, and adverse events related to the therapy were recorded. Relapses and its treatment were not addressed in this study. Follow-up time was defined as the period elapsed between the intervention and the last visit or death.

Outcome Measures

Primary outcomes were mortality, dialysis independence and eGFR 12 months after the therapeutic intervention. Secondary outcomes were mortality and eGFR at the end of follow-up.

Statistical Analysis

Differences between groups were evaluated with the Student's *t test* or Mann-Whitney *U* test, depending on

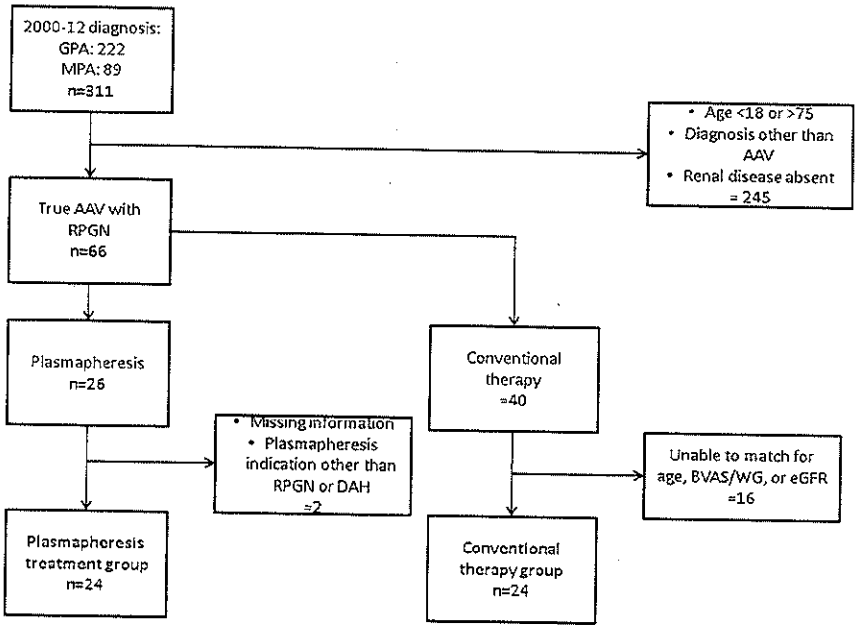

Fig. 1. Patient selection. GPA: Granulomatosis with polyangiitis; MPA: Microscopic polyangiitis; AAV: ANCA-associated vasculitis; RPGN: Rapidly progressive glomerulonephritis; DAH: Diffuse alveolar hemorrhage; BVAS/WG: Birmingham Vasculitis Activity Score for Wegener's Granulomatosis; eGFR: Estimated glomerular filtration rate.

the normality of data for continuous variables, and χ^2 test or Fisher's exact test for categorical variables as appropriate. Intention-to-treat analysis was performed to assess the number of patients free of dialysis 12 months after the intervention. McNemar's test was used on paired nominal data and survival curves were plotted using the Kaplan-Meier method for patients with and without plasmapheresis. Differences in estimated survival curves were calculated using the log-rank test. Patients lost to follow-up were censored from the survival analysis. Exact p-values are reported and two-sided p-value of ≤ 0.05 was considered statistically significant. All analyses were done using Stata software version 12.0 (StataCorp, TX) and SPSS version 20.0 (IBM SPSS Statistics).

RESULTS

Study Population

Forty-eight patients were included. Twenty-four of them received plasma exchange as supplement to the standard therapy with CYC and glucocorticoids while 24 were treated with conventional therapy alone. Length of follow-up since the intervention until the last visit or death in plasmapheresis patients was 25.2 ± 18.3 months and 71.3 ± 52 months in patients with standard treatment ($p = 0.004$). Patients were mainly female (54%), diagnosis of GPA was more prevalent than MPA (79%), and mean age at diagnosis was 48 years.

At the time of intervention median disease duration was less than a month in both groups. They were also similar in BVAS/WG score and eGFR at the time of intervention. Noteworthy, the FFS, a predictor for mortality in AAV patients at diagnosis, was also equal between groups. Despite the fact eGFR was similar between groups, more patients in the plasma exchange group were on dialysis at the time of intervention compared to patients with conventional therapy only (63% vs. 21%, $p = 0.004$). All patients presented with RPGN, and DAH was concomitantly present in 38% of the plasmapheresis group and 21% of the conventional therapy group ($p = 0.17$). Demographic and clinical characteristics are summarized in Table I.

Treatment

At the time of intervention, treatment between patients with and without plasmapheresis was similar, except for a higher frequency of high-dose (bolus) intravenous methylprednisolone administration (92% vs. 63%, $p = 0.018$) in patients that received plasmapheresis. Cumulative dose of CYC (11.2 ± 18.8 vs. 33.5 ± 41.4 g, $p = 0.03$) was lower in patients with plasma exchange.

Treatment during follow-up (after the initial intervention that required plasmapheresis) was also similar between groups except for a higher frequency of high-dose (bolus) intravenous methylprednisolone administration in patients who received plasma exchange (96%

TABLE I. Demographic and Clinical Characteristics

Variable	Plasma exchange $n = 24$	Conventional therapy $n = 24$	p
Demographic characteristics			
Female-*n* (%)	12 (50)	14 (58)	0.30
Age at diagnosis-years[a]	48.3 ± 17.9	48.3 ± 16.3	0.92
Smoking-*n* (%)	5 (21)	9 (38)	0.17
Diabetes mellitus-*n* (%)	4 (17)	2 (8)	0.33
Hypertension-*n* (%)	1 (4)	4 (17)	0.17
Dyslipidemia-*n* (%)	8 (33)	2 (8)	0.03
Disease characteristics			
GPA-*n* (%)	21 (88)	17 (71)	0.14
Disease duration at intervention-months[b]	0.47 (0-84.6))	0.11 (0-123.5)	0.11
eGFR at diagnosis-ml/min[a]	47 ± 43.1	50 ± 33.9	0.52
Dialysis at the time of intervention-*n* (%)	15 (63)	5 (21)	0.004
Alveolar hemorrhage-*n* (%)	9 (38)	5 (21)	0.17
BVAS/WG score at intervention[a]	13.2 ± 3.2	12.5 ± 2.8	0.52
Five-Factor Score at diagnosis[a]	1.4 ± 0.83	1.3 ± 0.90	0.75
Serologic characteristics at diagnosis			
c-ANCA positive-*n* (%)	19 (79)	15 (63)	0.17
p-ANCA positive-*n* (%)	3 (13)	8 (33)	0.08
Anti-PR3 positive-*n*/*N* (%)[c]	15/21 (71)	9/23 (39)	0.03
Anti-MPO positive-*n*/*N* (%)[c]	1/17 (6)	9/23 (39)	0.01
ESR (mm/h)[a]	78.4 ± 35.7	77.5 ± 29.1	0.64

[a]Mean values ± standard deviation.
[b]Median (minimum-maximum).
[c]N represents the number of patients tested for the antibodies.
ESR was determined in 18 patients with plasma exchange and 19 with conventional therapy.
GPA: Granulomatosis with polyangiitis; eGFR: Estimated glomerular filtration rate; BVAS/WG: Birmingham Vasculitis Activity Score for Wegener's Granulomatosis; c-ANCA: Cytoplasmic ANCA staining pattern; p-ANCA: Perinuclear ANCA staining pattern; Anti-PR3: Anti-proteinase 3 antibodies; Anti-MPO: Anti-myeloperoxidase antibodies; ESR: Erythrocyte sedimentation rate.

vs 63%, $p = 0.005$). Five patients (three in the plasmapheresis group and two in the conventional therapy group) didn't receive CYC at the time of intervention. These patients were critically ill and unstable at that moment to receive intensive immunosuppression. Indeed, three of four patients critically ill died in less than a month, and only one received CYC 7 months later. Patients who never received azathioprine either did not achieve full remission or were treated with oral CYC for remission maintenance. Rituximab is rarely used in our center due to economic constraints; only three patients in the conventional therapy group received this drug concomitantly with steroids and CYC. Treatment information is summarized in Table II.

Plasmapheresis

Patients underwent 5.5 ± 1.5 sessions, accounting for a total 137 sessions. Time since drug treatment initiation and plasma exchange prescription was 5.21 ± 4.13 days. Plasmapheresis was performed daily (four patients) or every other day (20 patients), with a fluid replacement ratio of 50 mL/kg, usually human albumin 5%, and rarely fresh frozen plasma (FFP) or hydroxyethyl starch. Complications associated to this therapy (16 events in total) were the following: coagulopathy requiring FFP infusion (six events), hypotension episodes requiring suspension of the procedure (five events), allergic reactions (three events), and symptomatic hypocalcemia (two events). Severe complications, such as cardiac arrest and catheter-associated infections were not observed.

Renal Outcome

After 12 months, both groups showed improvement in eGFR. In patients that received plasmapheresis and were alive at 12 months ($n = 18$) it improved from 19.0 ± 14.34 mL/minute at the time of intervention to 41.61 ± 37.7 mL/minute at 12 months ($p = 0.003$). In conventional therapy patients that were alive at 12 months ($n = 23$) it changed from 23.16 ± 14.71 mL/minute at intervention to 39.86 ± 25.67 mL/minute at 12 months ($p = 0.001$). No difference was found between groups ($p = 0.68$).

At the end of follow-up, eGFR in the plasma exchange group was still better than its baseline values, in 35.70 ± 30.06 mL/minute, $p = 0.005$. On the other hand, in the conventional therapy group, although still better than at baseline, eGFR was no longer statistically different (30.16 ± 22.01 mL/minute, $p = 0.15$). Again, no difference between groups was found ($p = 0.11$).

TABLE II. Treatment Characteristics

Variable	Plasma exchange $n = 24$	Conventional therapy $n = 24$	p
Treatment at the moment of intervention			
Methylprednisolone IV bolus -*n* (%)	22 (92)	15 (63)	0.018
Cyclophospamide-*n* (%)	21 (88)	22 (92)	0.50
Azathioprine-*n* (%)	1 (4)	1 (4)	0.75
Rituximab-*n* (%)	0	3 (13)	0.11
Drugs ever used, either at intervention or during follow-up			
Steroids-*n* (%)	24 (100)	24 (100)	-
Methylprednisolone IV bolus -*n* (%)	23 (96)	15 (63)	0.005
Cyclophospamide-*n* (%)	22 (92)	23 (96)	0.50
Azathioprine-*n* (%)	16 (67)	17 (70)	0.50
Cumulative doses			
Cumulative dose of prednisone-g[a]	24.2 ± 19.1	21.1 ± 10.5	0.98
Cumulative dose of Cyclophospamide-g[a]	11.2 ± 18.8	33.5 ± 41.4	0.03

[a]Mean values ± standard deviation.
g, grams.

TABLE III. Renal Outcome in Patients With Plasmapheresis and Conventional Therapy

Variable	Plasma exchange $n = 24$	Conventional therapy $n = 24$	p
eGFR (ml/min)[a]			
At diagnosis	47 ± 43.1	50 ± 33.9	0.52
At intervention	19 ± 14.34	23.16 ± 14.71	0.13
12 months after intervention	41.61 ± 37.77 ($n = 18$)	39.86 ± 25.67 ($n = 23$)	0.68
End of follow-up	35.70 ± 30.06	30.16 ± 22.01	0.78
Dialysis independence			
At 12 months-*n* (%)	12 (50)	22 (92)	0.001
End of follow-up-*n* (%)	13 (54)	14 (58)	1.00

[a]Mean values ± standard deviation.
eGFR: Estimated glomerular filtration rate.

At 12 months, three patients in each treatment group gained dialysis independence. In the plasmapheresis group, patients free of dialysis increased from 9/24 (38%) to 12/24 (50%), $p = 0.5$. Likewise, in the conventional treatment group the number of patients free of dialysis increased from 19/24 (79%) to 22/24 (92%), $p = 0.25$. The difference between groups at 12 months was significant $p = 0.001$. Table III summarizes the changes in renal function in patients with plasmapheresis and conventional therapy.

Mortality Outcome

Survival at 12 months after the intervention was 79% in the plasmapheresis group and 96% in the conventional therapy group ($p = 0.08$). At the end of follow-up, survival was 75% and 79%, respectively, without differences between groups ($p = 0.11$, log-rank). Six patients that received plasmapheresis died. Causes of death in this group were: infection, hemorrhagic stroke and alveolar hemorrhage, each occurring in two patients. Likewise, five patients in the conventional therapy group died and causes of death were infection (three patients), hemorrhagic stroke, and lethal arrhythmia (one patient each). Table IV summarizes the renal and mortality outcomes in both groups and Figure 2 shows the Kaplan-Meier survival curve in patients with and without plasmapheresis.

Adverse Events

Severe infections (requiring in-hospital treatment) diagnosed within the first 3 months after the intervention were frequent complications in both treatment groups. A tendency for a higher prevalence of these events was observed in patients treated with plasmapheresis (63% vs. 38%, $p = 0.07$).

DISCUSSION

In this retrospective analysis in clinical setting of 48 patients with recent onset AAV, mostly GPA with severe disease, our main findings were that both adjunctive plasma exchange and conventional therapy were associated with improvement in eGFR 12 months

TABLE IV. Outcomes at the End of Follow-up According to Treatment Group

Outcome	Plasma exchange $n = 24$	Conventional therapy $n = 24$	p
Alive, free of dialysis-n (%)	13 (54)	14 (58)	1.00
Alive, in dialysis-n (%)	5 (21)	5 (21)	1.00
Death, free of dialysis-n (%)	4 (17)	4 (17)	1.00
Death, in dialysis-n (%)	2 (8)	1 (4)	1.00

after the intervention, with a long-term benefit preserved in the plasmapheresis group only, although with a difference in the follow-up length. There was a significant difference in the percentage of patients free of dialysis after 12 months when plasmapheresis was compared with conventional therapy, although no significant difference was observed in the percentage of patients free of dialysis within each treatment group 12 months after intervention. Survival at 12 months and at the end of follow-up was similar between groups.

To compare both therapeutic regimens in this study, we decided to match patients according to the eGFR, considering that it is a better estimate of the renal function than the creatinine levels. Despite this fact, more patients in the plasmapheresis group were on dialysis at the time of intervention. We don't have an explanation for this difference, but it is important to remark that in the original report of the MEPEX trial [10] the inclusion criteria were based on the creatinine levels, and one of the most important results was the percentage of patients free of dialysis at 1 year.

We found that after 12 months some patients gained dialysis independence, an important change at the individual level, but this difference did not reach statistical significance in either group and both groups had an important improvement in the eGFR at one year. Regrettably, since most patients in the plasma exchange group were treated from 2009 onwards, a direct consequence of the publication of the MEPEX study in 2007 [10] and subsequent treatment guidelines [2,7–9], follow-up time was different between groups, making difficult to draw conclusions about the long term results.

It is important to mention that in a meta-analysis of the trials evaluating plasma exchange for renal vasculitis and RPGN, although a decreased risk of ESRD or death with plasma exchange was found, it was borderline (95% CI from 0.65 to 0.99; $p = 0.04$) [20], and a recent study in clinical settings with a similar design also failed to demonstrate a clear difference between patients treated with adjunctive plasma exchange [15]. This highlights the need to identify patients that could benefit from this therapeutic strategy.

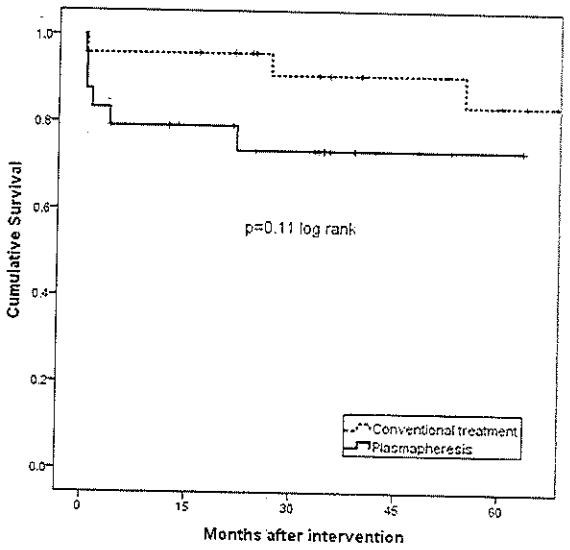

Fig. 2. Survival in patients with plasma exchange and conventional treatment.

Survival at 12 months and at the end of follow-up in our patients was 79% and 75% in the plasmapheresis group and 96% and 79% in the conventional therapy group respectively, without differences between groups. This mortality rate is concordant with the 82% and 76% cumulative survival at 1 and 5 years respectively reported in a retrospective multicenter study of patients with ANCA-associated renal vasculitis [21]. In this regard, our population presented severe disease manifestations, and negative prognostic factors for patient survival, such as reduced eGFR and higher BVAS [22].

Death directly attributable to activity of the disease was only noted in patients undergoing plasmapheresis: 2 patients with DAH, and one patient with ischemic stroke with hemorrhagic transformation in a woman without cardiovascular comorbidities or hypertension when the ischemic stroke occurred. This could have affected the 12-month mortality rate in the plasma exchange group, in which patients possibly presented a more severe course of the disease with greater organic compromise, including a higher frequency of DAH. Also, patients in the plasmapheresis therapy group were more frequently positive to anti-PR3 ANCA, a characteristic associated with extrarenal manifestations and higher inflammatory activity [21,23,24].

The lack of difference in mortality between groups is an important finding, since it is precisely in this category that benefit of plasmapheresis has been more elusive. Mortality in the MEPEX study was similar between treatment groups, both in the original study and its long-term follow-up [10,11]. Other recent retrospective studies have also failed to demonstrate better

survival in patients treated with plasma exchange [14,15]. Moreover, a meta-analysis of 9 trials including 387 patients concluded that plasma exchange may decrease the composite end point of ESRD or death in patients with renal vasculitis, but additional trials are required to support this given the limited data available [20].

Infections were the main cause of death in our population, as described previously in a large group of patients with recent diagnosis of AAV recruited in several European clinical trials [25].

Notwithstanding the early mortality related to infections and the higher infection rate observed in the plasma exchange group, we found that plasmapheresis use was relatively safe. The infectious processes were apparently unrelated to the procedure, since catheter-associated infections didn't occur. Furthermore, the adverse events directly related to plasmapheresis didn't alter the mortality outcome.

Certain considerations regarding the population studied and the prescription of treatment are pertinent. Patients with a more severe spectrum of the disease are referred to our tertiary care center, leading to possible selection bias where plasmapheresis is indicated in this critical clinical scenario. Also because of the low prevalence of these diseases, we considered a long period of observation (twelve years) that constitutes a long time span. Thus, treatment didn't follow a universal protocol in either group, but it was rather administered according to clinical judgment of the Rheumatologist and Nephrologist.

A definitive answer to whether plasmapheresis makes a difference in mortality and renal outcomes might only be addressed with large clinical trials, such as the ongoing international randomized controlled trial PEXIVAS [26].

However, this study adds information to the existing evidence where the benefit of plasmapheresis does not seem to be universal, highlights the need to be extremely careful in choosing patients that may benefit from this procedure and the need to establish protocols for the treatment of these patients.

CONCLUSIONS

To our knowledge, this is the first analysis of renal and survival outcomes in Hispanic patients with severe AAV treated with plasmapheresis. In this group of patients, mainly GPA, both plasmapheresis and conventional therapy improved eGFR at 12 months after intervention. Dialysis dependence and survival were similar between groups.

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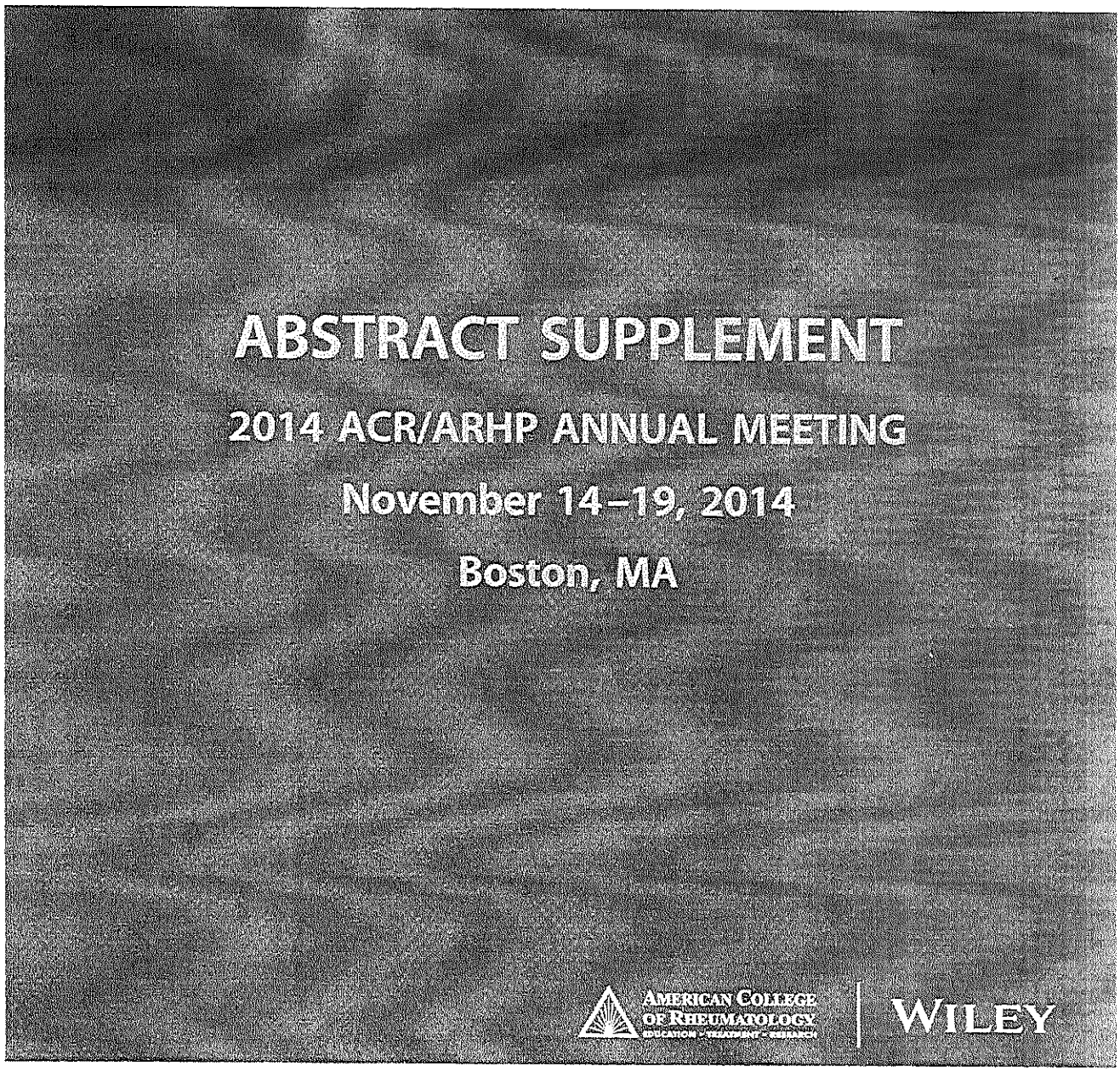

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ABSTRACT SUPPLEMENT

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carriage of SA and its small colony variants (SCV; intracellular SA with altered virulence phenotypes involved in chronic recurrent infection models) is unknown, respectively, during other ANCA-associated vasculitides (AAV), and those AAV and GPA.

Methods: All consecutive patients (09/2012–05/2013) with GPA, eosinophilic granulomatosis with polyangiitis (EGPA) or microscopic polyangiitis (MPA), followed at the French National Vasculitis Referral Center, and hospitalized patients, without vasculitis or specific risk factors for SA carriage (controls), were enrolled. All had bilateral anterior nasal swab cultures and SA-carriage frequencies were determined for each group. The French National Reference Center for Staphylococci identified the strains. Associations between SA nasal carriage and clinical manifestations, Birmingham Vasculitis Score (BVAS)-assessed disease activity, ANCA or C-reactive protein (CRP) level, and CTX impact on SA nasal carriage and BVAS were analyzed.

Results: A total of 119 AAV (GPA, n=80; EGPA, n=28; MPA, n=11) patients and 28 controls were enrolled. SA nasal carriage among the 3 AAV groups did not differ: 24 (30%) GPA, 8 (28.6%) EGPA and 3 (27.3%) MPA (P=0.971). Controls had non-significantly less frequent SA carriage (13.8%; P=0.39). SA-SCV phenotypes were identified in samples from 5/24 (20.8%) GPA, 1/8 (12.5%) EGPA and 2/3 (66.7%) MPA patients. SA nasal carriage was not significantly associated with number of prior relapse (P=0.866), BVAS (P=0.724), ANCA-positivity (P=0.657) or CRP level (P=0.340) for AAV, or GPA prior relapses (P=0.971) or BVAS (P=0.485). However, CTX use (usually as prophylaxis) was associated with a lower BVAS (P=0.029) and tended to be associated with a lower SA nasal carriage rate [9/43 (20.9%) patients on CTX vs 25/71 (35.2%) not on CTX: P=0.09].

Conclusion: Based on our results, SA nasal carriage did not differ among the AAV considered but seemed more frequent than in controls. Notably, CTX use, but not SA carriage, was associated with a lower BVAS and might reflect its intrinsic antiinflammatory rather than antimicrobial activity. Further bacterial analyses are needed to determine SA-strain susceptibility to CTX and identify known epidemic SA clones among those isolated from AAV carriers.

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Rituximab Versus Azathioprine for ANCA-Associated Vasculitis Maintenance Therapy: Impact in Health-Related Quality of Life. Grégory Pugnet[1], Christian Pagnoux[2], Alexandre Karras[3], Chahéra Khouatra[4], Olivier Aumaître[5], Pascal Cohen[1], Francois Maurier[6], Olivier Decaux[7], Jacques Ninet[8], Pierre Gobert[9], Thomas Quemeneur[10], Claire Blanchard-Delaunay[11], Pascal Godmer[12], Xavier Puéchal[1], Pierre-Louis Carron[13], Pierre-Yves Hatron[14], Nicolas Limal[15], Mohamed Hamidou[16], Eric Daugas[17], Thomas Papo[18], Bernard Bonnotte[19], Alfred Mahr[20], Benjamin Terrier[1], Philippe Ravaud[21], Luc Mouthon[1] and Loïc Guillevin[1]. [1]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP-HP, Université Paris Descartes, Paris, Paris, France, [2]University of Toronto, Toronto, ON, [3]Hôpital Européen Georges Pompidou, APHP, Paris, France, [4]CHU Louis Pradel, Lyon, Lyon, France, [5]Division of Internal Medicine, Centre Hospitalier Universitaire, Hôpital Gabriel Montpied, Clermont-Ferrand, Clermont-Ferrand, France, [6]Department of Internal Medicine, Metz, France, [7]Rennes University Hospital, Rennes, France, [8]Department of Nephrology and Internal Medicine, Hôpital Edouard Herriot, Lyon, France, Lyon, France, [9]Centre Hospitalier d'Avignon, Avignon, France, [10]CH, Valenciennes, France, [11]Hôpital de Niort, Niort, France, [12]Department of Internal Medicine, Centre Hospitalier Bretagne Atlantique de Vannes, Vannes, France, [13]Centre Hospitalier de Grenoble, Grenoble, France, [14]CHU Lille, Lille, France, [15]Hôpital Henri Mondor, APHP, Creteil, France, [16]CHU Hôtel Dieu, Nantes, Nantes, France, [17]AP-HP Hôpital Bichat, Paris, France, [18]Bichat Hospital, Paris, Paris, France, [19]INSERM UMR 1098, Besançon; University of Burgundy, Faculty of Medicine, IFR100; Department of Internal Medicine and Clinical Immunology, Dijon, France, [20]Hospital Saint-Louis, University Paris 7, Paris, France, [21]AP-HP Cochin Hospital, Paris, France.

Background/Purpose: A key goal in the management of ANCA-Associated Vasculitis (AAV) is to improve and preserve health-related quality of life (HRQOL). Several studies have found that patients with AAV have reduced HRQOL. We conducted a non-blinded, randomized- controlled, remission-maintenance trial (MAINRITSAN) to investigate the effects of rituximab versus azathioprine for AAV maintenance therapy on health-related quality of life.

Methods: In the phase III MAINRITSAN study, once complete remission was obtained for eligible patients (18–75 years old) with a combined glucocorticoid and pulse cyclophosphamide, 115 patients with newly diagnosed (2/3 of the enrolments) or relapsing (1/3) AAV, who fulfilled the American College of Rheumatology classification criteria(5) and/or the Chapel Hill Consensus Conference definition classification for AAV (6), were enrolled and randomly assigned, at a 1:1 ratio, to receive a 500-mg rituximab (RTX) infusion on D1, D15, 5.5 months later, then every 6 months for a total of 5 infusions over 18 months, or azathioprine (AZA) maintenance therapy for 22 months at the initial dose of 2 mg/kg/d. Mean changes every 3 months in SF-36 and HAQ from baseline to month 24 were analyzed. ClinicalTrials.gov, http://clinicaltrials.gov/, NCT00748644.

Results: Mean improvements in HAQ, from baseline to month 24 were statistically significantly greater in the rituximab group (−0.16 points) than in the control group (P = 0.038). As demonstrated by SF-36, baseline HRQOL in study patients was significantly impaired compared with age- and gender-matched US norms. At month 24, mean changes from baseline in SF-36 PCS scores trended to be greater in rituximab group (+3.95 points, P = 0.067) but surprisingly mean changes from baseline in SF-36 MCS were statistically significantly greater in azathioprine group (+4.23 points, P = 0.041).

Conclusion: Rituximab treatment to maintain AAV remission in the MAINRITSAN trial resulted in statistically significant but maybe not clinically meaningful improvement in physical functions.

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Plasmapheresis Therapy in ANCA-Associated Vasculitides: A Single-Center Retrospective Analysis of Renal Outcome and Mortality. David Solar-Cafaggi, Yemil Atisha-Fregoso and Andrea Hinojosa-Azaola. Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico.

Background/Purpose: ANCA-associated vasculitides (AAV) are rare, potentially fatal diseases with multiorgan involvement. Evidence for the use of plasmapheresis (PLEX) in patients with severe forms of AAV is limited and its long-term benefits on mortality and renal outcome are still unclear. The aim of our study was to evaluate renal outcome and mortality in clinical ground of AAV patients undergoing PLEX.

Methods: Retrospective study of patients with Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA) and positivity for MPO or PR3-ANCA antibodies attended at our center from 2000 to 2012. In 25 patients, PLEX was added to conventional therapy (high-dose steroids plus one or more immunosuppressants); they were compared with 25 patients treated only with conventional therapy without PLEX, matched for age (± 7 years), activity of disease (BVAS/GW, range ± 6) and glomerular filtration rate (GFR) (MDRD range ± 16 ml/min) at the time of intervention. Demographic data, comorbidities, clinical and laboratory characteristics were recorded. Outcome variables were mortality, dialysis dependence and GFR at 12 months. Statistics: Descriptive statistics, Student T-test, Mann-Whitney U-test, Chi-square, Fisher exact test, McNemar's test and Kaplan-Meier survival analysis, log-rank test, $p \leq 0.05$.

Results: Patients were mainly female (56%) and GPA (78%), mean age 47 years and BVAS/GW of 13. The only basal differences between patients with and without PLEX were more positivity for anti-PR3 (p=0.02), more frequency of methylprednisolone pulses ever (p=002) and lower accrued doses of CYP (p=0.01) in patients with PLEX. Main indication for PLEX was glomerulonephritis (96%).

At the time of intervention more patients in the PLEX group were on dialysis (p=0.02) and received concomitant methylprednisolone pulses (p=0.02) compared to patients without PLEX. At 12 months, both groups showed improvement in GFR before and after intervention (18.3±13.7 and 43.2±37.4 ml/min, p=0.001 in PLEX group; 23.5±14.5 and 39.6±25.1 ml/min, p=0.001 in conventional therapy group), but no difference was found between groups (p=0.85). No

differences were found in dialysis dependence between groups at 12 months (p=0.49), but more patients that completed one year of follow-up and were on dialysis at the time of intervention were free of dialysis at 12 months in the PLEX group (68% vs 32%, p=0.01) compared to patients without PLEX (20% vs 20%, p=1.0). Patients in the PLEX group presented more frequency of severe infections during the first 3 months (p=0.04). Survival at 12 months was 80% in the PLEX group and 96% in the conventional therapy group, with no differences in survival at outcome between groups (p=0.13, log-rank). Infection was the main cause of death in both groups.

Conclusion: In our population with AAV, both PLEX and conventional therapy improved renal function after the intervention, but no differences were found in dialysis dependence between groups at 12 months. Survival was similar in patients with and without PLEX, and infections were the main cause of death.

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Outcomes of Triple Therapy (Plasma Exchange, Cyclophosphamide and Systemic Corticosteroid) for Anti-Neutrophil Cytoplasm Antibody (ANCA)-Associated Vasculitis. Joanna Ueng[1], Katerina Pavenski[2] and Laurence Rubin[3]. [1]University of Toronto, Toronto, ON, [2]St. Michael's Hospital, Toronto, ON, [3]St. Michael Hospital, Toronto, ON.

Background/Purpose: Microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and Churg-Strauss Syndrome (CSS) are syndromes known as ANCA-associated vasculitis (AAV). In addition to immunosuppressive therapy, plasma exchange (PLEX) may be indicated in patients with pulmonary hemorrhage and/or severe renal insufficiency. However, PLEX may be associated with serious adverse effects such as infection. The objective of this study was to characterize and examine outcomes in patients with AAV treated with PLEX, in addition to corticosteroid and cytotoxic agents, at a major referral centre for PLEX.

Methods: A retrospective chart review was performed on all patients with AAV treated with PLEX at a major referral centre for PLEX between January 1, 2002 to May 31, 2012. Patients with GPA, MPA, CSS, systemic p-ANCA vasculitis, and systemic c-ANCA vasculitis were included while those with incomplete 3 and 12 month follow-up were excluded. Demographic, clinical, laboratory, and radiographic data from electronic and paper medical records were collected. Acute kidney injury (AKI) was defined as an increase in serum creatinine by ≥26.5 umol/L within 48 hours, or a ≥1.5 times increase above baseline serum creatinine within 7 days. Disease activity was assessed by the Birmingham Vasculitis Activity Score (BVAS) (v.3). Primary outcomes were survival at 1 year, dialysis dependence at 1 year, and dialysis dependence at 3 months from initiation of PLEX. The study was approved by the institution's Research Ethics Board.

Results: Forty-nine patients with AAV were treated with PLEX during the study period. Outcomes are reported for 48 patients, which excludes 4 patients lost to follow up and 2 patients with 3 and 12 month follow up that occurred outside the study period. 58% were male, and the median age was 59 years (range 25–83). This was the first presentation of AAV for 60%. GPA, MPA, CSS, systemic p-ANCA vasculitis, and systemic c-ANCA vasculitis was the primary diagnosis in 39%, 28%, 0%, 5%, and 28% of patients. Both pulmonary hemorrhage and AKI were present in 66%. The mean BVAS (v.3) score at presentation was 17.9. Triple therapy with systemic corticosteroid, cyclophosphamide, and PLEX occurred in 90%. Survival at 1 year, dialysis dependence at 1 year, and dialysis dependence at 3 months was 88%, 28%, and 37%, respectively. Renal recovery amongst those who were dialysis-dependent at presentation was 37% and 47% at 3 months and 1 year, respectively. Infection, bleeding (non-pulmonary hemorrhage), symptomatic hypotension, and catheter-related thrombosis occurred in 44%, 20%, 5%, and 2% of patients.

Conclusion: With triple therapy, 88% of patients with AAV survived at least 1 year. Almost 50% of patients who were dialysis-dependent on presentation experienced renal recovery after 1 year. An international randomized controlled trial is currently underway to investigate the specific role of PLEX in the treatment of AAV.

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Long-Term Outcomes Among Patients with Renal Disease Secondary to ANCA-Associated Vasculitis: Temporal Trends over 25 Years. Rennie L. Rhee[1], Susan L Hogan[2], Caroline J. Poulton[2], Julie Anne G. McGregor[2], J. Richard Landis[1], Ronald Falk[2] and Peter A. Merkel[3]. [1]University of Pennsylvania, Philadelphia, PA, [2]UNC Kidney Center, Chapel Hill, NC, [3]Vasculitis Center, University of Pennsylvania, Philadelphia, PA.

Background/Purpose: Significant advances have been made in the diagnosis and treatment of patients with ANCA-associated vasculitis (AAV). However, little is known about how these advances have changed long-term outcomes especially among patients with renal involvement. The objective of this study was to examine temporal changes of long-term outcomes, including the impact of early diagnosis and duration of cyclophosphamide use in AAV.

Methods: An inception cohort of patients with AAV from the Glomerular Disease Collaborative Network diagnosed from 1985 and 2009 was evaluated. All patients had a positive test for ANCA and a renal biopsy consistent with AAV. Patients were categorized into 5-year time periods based on year of diagnosis. The primary outcome was occurrence of end-stage renal disease (ESRD) or death in 5 years; secondary outcome was occurrence of relapse in 5 years. Kaplan-Meier estimates, Cox proportional hazard models, and linear contrasts were used for analysis. Models were adjusted for age, sex, race, diagnosis (granulomatosis with polyangiitis, microscopic polyangiitis, or renal-limited vasculitis), ANCA type (C-PR3 or P/MPO), site (tertiary care or community practice), duration of disease before biopsy, extra-renal organ involvement, and serum creatinine (SCr) at time of diagnosis. In a subgroup of patients with no event by 12 months, duration on cyclophosphamide (CYCdur, months) up to 12 months was also included.

Results: Data was available on 568 patients who met the inclusion criteria. Across the 5 time periods, there were no significant differences in baseline characteristics or duration of follow-up; however, over time increasing proportions of patients were managed in a tertiary care center and baseline SCr decreased (**Table**). There was a decreasing 5-year risk of ESRD or death across the time periods and an increasing 5-year risk of relapse, p for trend < 0.001 (**Figure**). After adjustment for baseline characteristics, the risk of relapse was similar between the time periods (p for trend = 0.698) but the risk of ESRD or death continued to decrease over time (p for trend = 0.008). SCr was the only significant predictor of decreasing risk of ESRD or death (HR 1.14, 95% CI 1.08–1.21, P<0.001) while CYCdur was not associated with risk of ESRD or death.

Conclusion: In patients with AAV, over 25 years, the risk of ESRD or death decreased and the risk of relapse has not changed. A lower SCr at diagnosis, a potential marker of earlier disease detection, is the strongest predictor of improvement in risk of ESRD or death.

Table: Patient characteristics at diagnosis

Characteristic	All	Time Period 85–89	90–94	95–99	00–04	05–09	p-value for trend
N	568	98	141	176	102	51	
Median age, years (IQR)	60 (46–70)	61 (52–70)	61 (42–68)	60 (48–72)	59 (47–73)	58 (48–68)	0.72
Female, %	42%	47%	52%	46%	40%	42%	0.5
Race, %	88%	85%	94%	91%	84%	78%	0.17
White	9%	14%	5%	7%	6%	6%	0.68
Black	3%	1%	1%	2%	9%	12%	0.01
Other							
Diagnosis, %	20%	18%	21%	23%	20%	25%	0.62
GPA	55%	60%	49%	54%	56%	57%	0.68
MPA	24%	25%	30%	23%	24%	18%	0.48
RLV							
ANCA ELISA, %	41%	44%	36%	44%	41%	39%	
PR3-P	59%	56%	65%	56%	59%	54%	0.95
MPO-C							
Organ involvement, %	59%	58%	61%	60%	62%	53%	0.49
Lung	41%	35%	35%	43%	46%	47%	0.04
Joint	29%	36%	26%	32%	33%	41%	0.05
Upper respiratory	22%	22%	29%	23%	19%	18%	0.52
Skin	11%	15%	16%	12%	8%	4%	0.03
GI	10%	14%	9%	11%	8%	2%	0.03
Neurologic	5%	6%	7%	2%	3%	0%	0.05
Muscle							
Mean serum creatinine, mg/dl (SD)	4.5 (3.5)	5.9 (4.1)	4.9 (3.7)	4.2 (3.4)	3.9 (3.2)	3.5 (2.9)	<0.001
Duration of follow-up, median months (IQR)	31 (11–60)	33 (13–60)	31 (7–72)	25 (7–48)	29 (14–51)	33 (11–55)	0.78
Tertiary care, % (vs community practice)	38%	31%	27%	41%	54%	62%	<0.001

*Test of significance for linear contrast of 5 time periods.
GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; RLV: renal limited vasculitis.