Rev. Colomb. Nefrol. 2014; 1(1): 3 -9. http//www.revistanefrologia.org

Scientific Research Article

http://dx.doi.org/10.22265/acnef.1.1.167

Therapeutic plasma exchange in patients with pauciimmune vasculitis: Hospital Universitario San Ignacio experience; Bogotá, Colombia

Juan P. Córdoba[1], Kateir Contreras[1], Maite Hurtado[1], Jessica Pinto[1], Martha P. Rodríguez[1], Carolina Larrarte[2]

[1] Unidad de Nefrología, Hospital Universitario San Ignacio, Bogotá, Colombia
[2] Unidad Renal, RTS - Agencia Santa Clara, Bogotá, Colombia

Abstract

Introduction: The vasculitis ANCAS positive, are a group of diseases with different clinical manifestations. Therapeutic plasma exchange has become an excellent tool for the treatment of these patients in specific conditions. Objective: Describe the demographic and clinical characteristics of patients and the final outcomes in patients with positive ANCAS vasculitis that required therapeutic plasma exchange (TPE).

Materials and methods: All patients under 18 years old with positive ANCAS vascultiis that required TPE where included during the period of May 2010 and December 2013.

Results: 13 patients where treated, with a total of 73 TPE sessions. The average age was 52,3 years (Range 17 to 70). The principal diagnosis for interventions was rapidly progressive glomerulonephritis (RPGN) plus alveolar hemorrhage (63%). The average number of sessions per patient was 5,6 (range 1 a 10) with an average of plasma volume exchange per session of 1,26 (range 0.72 a 1,56). Of the 13 patients, 11 (84,6%) required renal replacement therapy (RRT) during hospitalization. At discharge, 36.3% recover the renal function, 27% continue on RRT and 36,3% died. There was at least one complication in 6,8% of all sessions.

Conclusions: TPE is an excellent tool to treat patients with positive ANCAS vasculitis that present with RPGN, high levels of serum creatinine or dialysis need, or alveolar hemorrhage. This is a safe procedure with comparable results according to International literature.Key words: Apheresis, plasmapheresis, therapeutic plasma exchange, vasculitis, ANCA.

Key words: Apheresis, plasmapheresis, therapeutic plasma exchange, vasculitis, ANCA

Plasmaféresis y vasculitis pauciinmune: experiencia Hospital Universitario San Ignacio, Bogotá, Colombia

Resumen

Introducción: Las vasculitis asociadas a anticuerpos contra el citoplasma de los neutrófilos (ANCA) son un grupo de enfermedades con una presentación clínica variada. La plasmaféresis (PMF), se ha convertido en una herramienta más de manejo para estos pacientes.

Objetivo: Describir las características demográficas, clínicas y los desenlaces finales de los pacientes con diagnóstico de vasculitis pauciinmune que requirieron manejo con PMF.

Materiales y métodos: Se incluyeron todos los pacientes mayores de 18 años con diagnóstico de vasculitis pauciinmune (biopsia renal o ANCA) que requirieron PMF, durante el período comprendido entre mayo de 2010 hasta diciembre de 2013.

Recibido:5 de mayo de 2014 - Aceptado: 15 de mayo de 2014

Correspondencia: Juan P. Córdoba, jpcordoba@husi.org.co

Resultados: Se intervinieron 13 pacientes, realizándose en total 73 sesiones de PMF. La edad promedio fue 52,3 años (rango 17 a 70). El principal diagnóstico para intervención fue glomerulonefritis rápidamente progresiva (GNRP) más hemorragia alveolar (63%). El promedio de sesiones por paciente fue 5,6 (rango 1 a 10) con un promedio de recambios plasmáticos por sesión de 1,26 (rango 0.72 a 1,56). De los 13 pacientes, 11 (84,6%) requirieron terapia de reemplazo renal (TRR) durante la hospitalización. Al egreso 36,3% recuperó la función renal, 27% continuó con TRR y 36,3% falleció. Se presentó al menos una complicación en 6,8% de las sesiones.
Conclusiones: La PMF es una herramienta terapéutica necesaria en pacientes con vascultis ANCA positiva que cursen con GNRP, coexistencia de enfermedad antimembrana basal glomerular o hemorragia alveolar severa. Es un procedimiento seguro, con resultados comparables y estudios internacionales publicados.

Palabras clave: Aféresis, plasmaféresis, intercambio plasmático, vasculitis, ANCA.

Introduction

The anti-neutrophil cytoplasmic associated vasculitis (ANCAS) include the granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis), microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis (also known as Churg Strauss syndrome) and the vasculitis confined to the kidney.[1,2]The clinical presentation is variable, with a spectrum ranging from the insidious instauration of renal failure, preceded by symptoms similar to those of a viral infection given by arthralgias, myalgias, low grade fever, to the accelerated deterioration of the renal function with hematuria, cylindruria and proteinuria, and even requiring renal replacement therapy, being a potentially fatal condition when associated with alveolar hemorrhage.[1]

Renal involvement in vasculitis is frequent, greater than 50% at the time of diagnosis and of 70 to 85% during the course of the disease.[1]

TPE has become an additional tool for the management of these patients, demonstrating its benefit, mainly, in 3 scenarios: rapidly progressive glomerulonephritis (RPGN), coexistence of anti-glomerular basement membrane disease, and severe alveolar hemorrhage. The rational of the use of TPEin this pathology is that the ANCAS, mainly involvedin the pathophysiology, are molecules of high molecular weight, low volume of distribution, and a long half-life, that allow to be effectively removed by this therapy.

This work aims to show the experience of the group of the San Ignacio University Hospital in the management of patients with pauciimmune vasculitis with TPE, describing the demographic and clinical characteristics, the outcomes of the patients and the technical properties of the therapy. To our knowledge, this would be the first series of cases at the national level that has been reported in the medical literature, contributing to knowledge about the behavior of this disease in our population.

Objectives

To describe the demographic and clinical characteristics and the outcomes of the patients with a diagnosis of pauciimmune vasculitis who required management with TPEand to describe the technical properties of such therapy in the San Ignacio University Hospital, in the period between May 2010 and December 2013.

Materials and methods

All patients older than 18 years with a diagnosis of pauciimmune vasculitis (renal biopsy or ANCA) who required TPE according to the current international indications (creatinine ≥5.7 mg/dL, need for dialysis, alveolar hemorrhage), managed by the apheresis group of the San Ignacio University Hospital were included. The information was obtained

from the Integrated Hospital Management System (SAHI, by its initials in Spanish: Sistema de Administración Hospitalaria Integrado) and was recorded in the database created in Excel program. Descriptive analyzes of the sociodemographic and clinical characteristics of the study population were performed. Absolute and relative frequency measures were usedfor the categorical variables, and measures of dispersion and central tendency for the continuous variables.

Results

In the observed period, 13 patients were intervened, conducting in total 73sessions of TPE. The average age was 52.3 years (range 17 to 70), 46.1% of patients were older than 65 years and 53.8% were male. The main indication for TPEwas RPGN plus alveolar hemorrhage (63%) (Table1). All patients had positive ANCA, of these,53.8% were p-ANCA and 46.1% c-ANCA. Measurements of anti-glomerular basement membrane antibodies were carried out to 8 patients, which were negative. 54% had positive antinuclear antibodies, ANA, of these, 71%with speckled pattern and the remaining were homogeneous. Only one of the patients had complement (C4) consumption.

93% of the patients had renal and pulmonary involvement; no more than one patient had only alveolar hemorrhage. The average number of sessions per patient was 5.6 (range 1 to 10) with an average of plasma volume exchanges per session of 1.26 (range 0.72 to 1.56). The replacement solution used most frequently was fresh frozen plasma (53.5% of sessions) followed byalbumin5% in 39.7% (Table 2). Temporary catheters for hemodialysis were used in all cases as vascular access, 42% of jugular location and58% in the femoral vein. The majority of sessions (68.5%) were carried out in the intensive care unit (ICU), the remaining in the general ward. Transmembrane filtration technique was used in the 100% of sessions.

In five sessions (6.8%) there was at least one complication. There were 7 complications in total that occurred in two patients. The majority of complications were related to the vascular access, in 5 sessions there was catheter dysfunction and in one a minor bleeding episode. One patient had an infection related to the vascular access.

In more than 80% of plasmapheresis sessions, the values of calcium and potassium, before initiation of the therapy, were normal and 75% were compatible with hyperphosphatemia (Table 3).

The electrolytes tests performed to the patients during the time they were on treatment with TPE were recorded. The records of calcium and potassium had a similar distribution, 12% of the records of calcium indicated hypocalcemia. About half of the records were compatible with hypermagnesemia (Figure 1).

All patients received cyclophosphamide and corticosteroids as part of the medical management. Of the 13 patients, 11 (84.6%) required renal replacement therapy (RRT) during the hospitalization, 10 due to acute kidney injury (AKI) associated with ANCA positivevasculitis and one was on chronic dialysis and was admitted due to alveolar hemorrhage secondary to p-ANCA vasculitis. Half of the 10

Table 1

Diagnoses, patients and number of sessions

Diagnosis	Sessions No.	Sessions %	Patients No	Session/Patient	Procedures No.	Procedures %
RPGN plus alveolar hemorrhage	46	63.0	8	5.8	8	61.5
RPGN without alveolar hemorrhage	23	35.6	4	6.5	4	30.8
Alveolar hemorrhage without RPGN	1	1.4	1	1.0	1	7.7
Total	73	100.0	13		13	100.0

RPGN: Rapidly progressive glomerulonephritis.

Table 2

Number of sessions according to diagnosis and replacement liquid used

Diagnosis	Alb 5% (%)	Plasma (%)	Plasma + Alb (%)	Total (%)
RPGN plus alveolar hemorrhage	9 (19.5)	32 (69.5)	5 (11)	46 (100)
RPGN without alveolar hemorrhage	20 (77)	6 (23)	0	26 (100)
Alveolar hemorrhage without RPGN	0	1 (100)	0	1 (100)
Total	29 (39.7)	39 (53.5)	5 (6.8)	73 (100)

RPGN: Rapidly progressive glomerulonephritis. Alb: albumin

Table 3

Measurement of electrolytes previous to initiation of plasmapheresis

Electrolytes	Evaluated Proc No %	Average value (SD)	Normal %	Low %	High %
Calcium	10 (77)	9.46 (0.77)	90%	0%	10%
Potassium	7 (54)	4.09 (0.38)	86%	14%	0%
Phosphorus	8 (62)	5.48 (1.79)	25%	0%	75%
Magnesium	13 (100)	2.2 (0.31)	54%	0%	46%

Total of procedures 13 SD: Standard deviation

patients who required dialysis because of the vasculitis, died. Of the remaining 5 patients, 3 continued requiring dialysis upon hospital discharge.

Six patients died. The cause of death in 75% of cases was sepsis and in 25% respiratory failure secondary to alveolar hemorrhage.

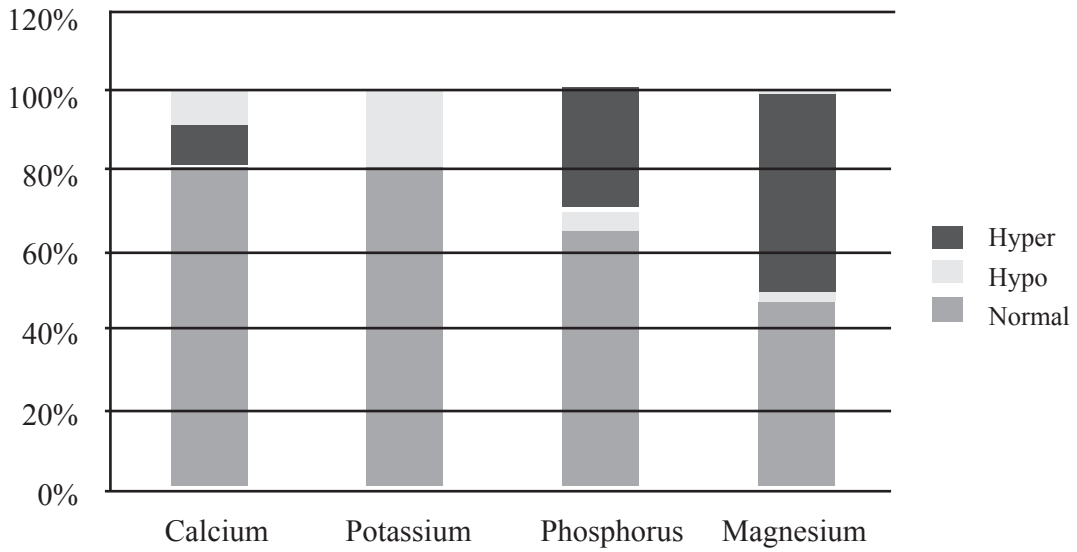
Discussion

The annual incidence of this disease is around 5-20 cases per million inhabitants and it varies from one region to another. It has a greater predilection for patients older than 50 years and there is no difference between sexes in the affected patients. Renal involvement in ANCA vasculitis is frequent, occurring in 50% of patients at the time of diagnosis and in between 70% and 85% during the course of the disease.[1] The prognostic factors are the promptnesswith which the treatment begins, the renal function at the time of diagnosis and the extent of the commitment in the renal biopsy.[3] This commitment can be mild to severe and the involvement described as severe usually is an indication for TPE.

The objective of the treatment is to induce complete remission which is defined as the absence of active disease, however, many definitions are found in the literature.[4,5]

This descriptive study aims to demonstrate the experience of the Hospital in the intervention with TPEin patients with ANCA positive vasculitis. For this reason, it does not allow to establish the percentage of patients with pauciimmune vasculitis with renal involvement, since it is part of a sample of patients which requires intervention with TPEand not the population with vasculitis in general.As reported in medical literature, the majority of patients intervened were older than 50 years and there were no differences between sexes.[1]

Figure 1
Measurement of electrolytes during the plasmapheresis sessions



The clinical studies demonstrate that in pauciimmune vasculitis, 50% to 75% of patients have positive ANCAS.[6] All patients registered in this study had positive ANCAS because it was used as a diagnostic criterion of the disease. TPEhas not been carried out in the institution to patients with histopathological diagnosis without ANCA positivity.

The treatment of ANCA vasculitis with systemic involvement should be timely in order to avoid medium and long-term complications such as loss of renal function, requirement for renal replacement therapy, alveolar hemorrhage and even death. The treatment consists of 2 phases, induction and maintenance.[1] Cyclophosphamide is the drug of first choice in the induction phase.[7] The patients reported in this study had severe and systemic commitment requiring induction immunosuppressive treatment for which they received cyclophosphamide associated with steroid. This study was not intended to describe the next phases of treatment or the presence or absence of remission, so no emphasis was givenon this aspect, but on the response to the TPE.

The mortality of patients with ANCA vasculitis with systemic involvement is high.[8] It is worth highlighting that renal involvement and alveolar hemorrhage are markers of poor prognosis, which explains the mortality of about half of the patients in the study. Since the follow-up of the patients is carried out until discharge, it is not possible to know the dependence on renal support or the extrahospitalary mortality.

TPE has become a therapeutic tool for these patients and has been evaluated in several clinical studies. Two studies assessed the efficacy of plasma exchange in patients with severe active kidney disease, 48 patients with focal necrotizing GMN were assigned to immunosuppressive therapy with or without TPE, without finding differences between the patients who had creatinine lower 5.7 mg/dL or in those who had a higher value but did not require dialysis, instead, it showed benefit in those who required dialysis.[9] The MEPEX study included patients with diagnosis of pauciimmune glomerulonephritis and a serum creatinine of about 5.7 mg/dL, with an average of 8.3 mg/dL, and it showed that the therapy with TPE is

associated with a greater likelihood of dialysis-free renal survival at 3 months (69% vs. 49%), and reduction of the risk of progression into terminal chronic kidney disease at 1 year (19 vs. 43%).[10] In cases of alveolar hemorrhage there are not controlled randomized clinical trials, but this therapeutic strategy has theoretical support in this scenario, and it is the benefit provided by the removal of ANCAS and the outcomes obtained in patients with anti-glomerular basement membrane disease.[11,12] In the San Ignacio University Hospital the interventions with TPEto the patients with positive ANCA vasculitis are conducted according to the recommendations of the ASFA international guidelines for apheresis;[13] the indications have been noted previously in this paper.

As for the technique of TPE, all sessions were performed with the transmembrane filtration technique. The replacement solution most frequently used in this record was fresh frozen plasma. The indications for this replacement solution are specific and they include active bleeding or the risk to present it due to coagulopathy associated to the therapy. The use of fresh frozen plasma during the therapy of these patients is explained by the type of population intervened and the percentage of patients with alveolar hemorrhage.

The international guidelines for apheresis recommend to perform 1 to 1.5 plasma volume exchanges in each session and to carry out the TPEdaily or every other day for a total of 6 to 9 sessions according to indication.[13] In the institution, the prescription of the therapy is carried out under the same number of plasma exchanges and the periodicity and timing of the therapy is defined according to the response to management, the clinical condition of the patient and the adverse events of the therapy such as the presence of coagulopathy.

The treatment with TPEis safe, being documented a low percentage of sessions with complications. Most of these were related to vascular access. No arterial hypotension or allergic reactions, which are adverse events reported frequently in the literature, weredocumented in any session of TPE.

The hypocalcemia is attributed to the TPEand the type of replacement solution used, the hyperphosphatemia is not associated to the therapy and the experience of the group has documented this finding in the patients intervened with TPE who have concomitant renal dysfunction.[14] The hypermagnesemia can be explained by the administration of magnesium sulfate that was used, at that time, as protocol for TPE in the institution. Since electrolytic alterations are documented before and during the therapy with TPE, it is important to carry out a follow-up and an individualized management of the electrolytes.

Currently, is ongoing the study Plasma Exchange and Glucocorticoids for Treatment of Anti-Neutrophil Cytoplasm Antibody (ANCA) - Associated Vasculitis (PEXIVAS), whose objective is to determine if plasma exchange is effective in reducing the rates of death and terminal chronic kidney disease, the results are expected for the year 2016.[15]

Conclusion

Positive ANCA vasculitis that occurswith RPGN, coexistence of anti-glomerular basement membrane disease or severe alveolar hemorrhage, would benefit from therapeutic plasmapheresis. It is a safe procedure, with a percentage of complications of6.8% in our group. The clinical results and outcomes found were similar to those reported in the world literature. 84.6% required renal replacement therapy during hospitalization. 36.3% recovered the renal function at discharge and 27% continued with RRT. The intrahospital mortality was 36.3%. The above ratifies that TPEis needed as an additional treatment tool for this type of patients.

Conflict of interest.

The authors declare they do not have any conflict of interest.

Bibliographic references

1. Ponticelli, C., Glassock, RJ. Treatment of Primary Glomerulonephritis. Second Edition. Oxford University Press. Chapter 10, pag 399-426.
2. Falk RJ, Gross WL, Guillevin L, Hoffman GS, Jayne DR, Jennette JC, Kallenberg CG, Luqmani R, Mahr AD, Matteson EL, Merkel PA, Specks U, Watts RA; American College of Rheumatology; American Society of Nephrology; European League Against Rheumatism.Granulomatosis with polyangiitis (Wegener's): an alternative name for Wegener's granulomatosis. Arthritis Rheum. 2011 Apr;63(4):863-4.
3. 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. 2005 Nov 1;143(9):621-31. PubMed PMID: 16263884.
4. Miloslavsky EM, Specks U, Merkel PA, Seo P, Spiera R, Langford CA, Hoffman GS, Kallenberg CG, St Clair EW, Tchao NK, Viviano L, Ding L, Sejismundo LP, Mieras K, Iklé D, Jepson B, Mueller M, Brunetta P, Allen NB, Fervenza FC, Geetha D, Keogh K, Kissin EY, Monach PA, Peikert T, Stegeman C, Ytterberg SR, Stone JH; Rituximab in ANCA-Associated Vasculitis-Immune Tolerance Network Research Group. Clinical outcomes of remission induction therapy for severe antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2013 Sep;65(9):2441-9.
5. Stone, JH., Kaplan, AA., Falk,RJ. Initial immunosuppressive therapy in granulomatosis with polyangiitis and microscópico polyangiitis Last updated: Agosto 26, 2013. Uptodate 2014.
6. Lionaki S, Blyth ER, Hogan SL, Hu Y, Senior BA, Jennette CE, Nachman PH, Jennette JC, Falk RJ. Classification of antineutrophil cytoplasmic autoantibody vasculitides: the role of antineutrophil cytoplasmic autoantibody specificity for myeloperoxidase or proteinase 3 in disease recognition and prognosis. Arthritis Rheum. 2012 Oct;64(10):3452-62. doi: 10.1002/art.34562. PubMed PMID: 23023777.
7. 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. 2012 Jun;71(6):955-60. doi: 10.1136/annrheumdis-2011-200477. Epub 2011 Nov 29
8. Nachman PH, Hogan SL, Jennette JC, Falk RJ. Treatment response and relapse in antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. J Am Soc Nephrol. 1996 Jan;7(1):33-9.
9. Pusey CD, Rees AJ, Evans DJ, Peters DK, Lockwood CM. Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies. Kidney Int. 1991 Oct;40(4):757-63.
10. 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. 2007 Jul;18(7):2180-8. Epub 2007 Jun 20.
11. Walsh M, Catapano F, Szpirt W, Thorlund K, Bruchfeld A, Guillevin L, Haubitz M, Merkel PA, Peh CA, Pusey C, Jayne D. Plasma exchange for renal vasculitis and idiopathic rapidly progressive glomerulonephritis: a meta-analysis. Am J Kidney Dis. 2011 Apr;57(4):566-74.
12. Gallagher H, Kwan JT, Jayne DR. Pulmonary renal syndrome: a 4-year, single-center experience. Am J Kidney Dis. 2002 Jan;39(1):42-7.
13. Schwartz J, Winters JL, Padmanabhan A, Balogun RA, Delaney M, Linenberger ML, Szczepiorkowski ZM, Williams ME, Wu Y, Shaz BH. Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the Writing Committee of the American Society for Apheresis: the sixth special issue. J Clin Apher. 2013 Jul;28(3):145-284.
14. Córdoba J.P., et al. Plasmaféresis terapéutica. Acta Médica Colombiana, 2014, enero-marzo: (39)29-34.
15. http://clinicaltrials.gov/show/NCT00987389