Scientific Research Publishing

Open Journal of Nephrology, 2022, 12, 195-202
https://www.scirp.org/journal/ojneph
ISSN Online: 2164-2869
ISSN Print: 2164-2842

ANCA-Associated Vasculitis: Value of Apheresis in Initial Treatment

Djibrilla Bonkano[1], Hassane Moussa Diongolé[2,3], Hamza Naciri Bennani[4], Johan Noble[4,5], Paolo Malvezzi[4], Lionel Rostaing[4,5]

[1]Amirou Boubacar Diallo National Hospital of Niamey, Niamey, Niger
[2]National Hospital of Zinder, Zinder, Niger
[3]Faculty of Health Sciences of Zinder, Zinder, Niger
[4]Nephrology, Hemodialysis, Apheresis and Kidney Transplantation Department, Université Hospital Grenoble, Grenoble, France
[5]Université Grenoble Alpes, Grenoble, France
Email: hnaciribennani@chu-grenoble.fr, jnoble@chu-grenoble.fr, lrostaing@chu-grenoble.fr

How to cite this paper: Bonkano, D., Diongolé, H.M., Bennani, H.N., Noble, J., Malvezzi, P. and Rostaing, L. (2022) ANCA-Associated Vasculitis: Value of Apheresis in Initial Treatment. *Open Journal of Nephrology*, **12**, 195-202.
https://doi.org/10.4236/ojneph.2022.122019

Received: March 21, 2022
Accepted: May 16, 2022
Published: May 19, 2022

Abstract

Introduction: Vasculitis associated with anti-neutrophil cytoplasm antibodies (ANCA) can be grouped with granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MAP), and eosinophilic granulomatosis with polyangiitis (EGPA). Diagnosis of these rare pathologies is based on clinical presentation, the positivity of ANCA, and, if possible, histological proof of vasculitis. Our study describes a series of six cases of ANCA-associated vasculitis where due to the severity of symptoms apheresis sessions were started from the beginning of the therapy. **Patients and methods:** We conducted a retrospective, single-center observational, monocentric study on all patients treated by apheresis for ANCA vasculitis in the period January 01, 2016 to December 01, 2019. **Results:** We identified six cases of ANCA vasculitis treated by apheresis over a 3-year period. The mean age was 61 ± 19 years; M/F gender ratio was 1:1. Initial renal damage in all patients was rapidly progressive glomerulonephritis. Inflammatory syndrome occurred in all patients with average CRP of 82 mg/L. All patients had positive ANCA at diagnosis. Four patients required renal replacement therapy at the time of diagnosis. The induction regimen consisted of rituximab associated with IV boluses of methylprednisolone. The apheresis techniques used were the same for all patients, *i.e.* plasmapheresis. Outcomes were favorable for five patients; only one patient became dependent on hemodialysis. No mortality occurred. **Conclusion:** This study analyzed practices for the management of patients with ANCA vasculitis. No patient was treated with cyclophosphamide as a first approach but rituximab instead. Plasmapheresis was given because of symptoms severity at initial diagnosis.

Keywords

ANCA-Associated Vasculitis, Apheresis, Rituximab, Remission, Rapidly Progressive Glomerulonephritis

1. Introduction

ANCA-associated vasculitides are necrotizing vasculitis that affects small-caliber vessels and the condition comprises three clinical entities: granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis [1]. ANCA vasculitis is a rare disease, with prevalence in Europe of between 46 - 184 cases per million inhabitants [2] [3]. Renal involvement is noted in more than 50% of cases, usually manifesting as rapidly progressive renal failure with proteinuria and hematuria. Its diagnosis is evoked by the positivity of the ANCA, but also from extra-renal signs (fever, arthritis, myalgia, hemoptysis, purpura, neuropathy, biological inflammatory syndrome). A renal biopsy confirms necrotizing glomerulonephritis with pauci-immune extra-capillary epithelial proliferation without immunoglobulin deposits or complement to immunofluorescence [4]. The evolution of these pathologies without treatment leads to death; with treatment, the prognosis can be improved considerably.

Treatment is based on induction therapy followed by maintenance therapy. During the induction phase, corticosteroid therapy must be combined in most cases with cyclophosphamide or rituximab. The maintenance phase aims to prevent a relapse, which is particularly frequent in cases of ANCA anti-proteinase 3 (anti-PR3), and is based on rituximab therapy, the optimal duration of which still needs to be defined [5].

2. Patients and Methods

We conducted a retrospective, observational, monocentric study that included all patients treated by apheresis for ANCA vasculitis. The study was conducted in the nephrology, hemodialysis and apheresis department of our University Hospital in the period from January 01, 2016 to December 01, 2019. In order to do so, we reviewed our medical charts from that period by searching cases using the words ANCA-associated vasculitis and apheresis. Remission was defined as an absence of evidence of disease activity attributable to active vasculitis. Refractory forms were defined by an active and progressive disease that did not respond after 4 weeks of conventional treatment. Lack of response was defined as ≤50% reduction in Vasculitis Activity Score (BVAS) after 6 weeks of treatment. Chronic persistent disease was defined as the presence of at least one major item or three minor items on the Disease-Activity Score, e.g., BVAS or BVAS/WG after at least 12 weeks of treatment [6]. We used the BVAS (Birmingham Vasculitis Activity Score, version 2003) to assess the activity of vasculitis, the VDI (Vasculitis Damage Index) to assess sequelae related to vasculitis, and the FFS (Five-Factor

Score, revised in 2011) to assess the factors impacting survival with vasculitis.

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by CNIL (French National Committee for data protection; approval number 1987785v0). The biobank collection number is BRIF BB-0033-00069. All data are available upon request to the corresponding author.

3. Results

We identified six cases of ANCA vasculitis treated by apheresis over a 3-year period. The patients' mean age was 61 ± 19 years and M/F gender ratio was 1:1. Table 1 summarizes the patients' data.

Three patients presented with a deteriorating condition with fever and polyarthralgia. One patient presented with vascular purpura-type skin involvement. Only one patient presented with pericardial involvement. One patient in the anti-PR3 group presented with ophthalmologic involvement, *i.e.*, episcleritis. Two patients presented with ENT disorders: one had epistaxis and scabs, and the second had otitis associated with right-ear deafness. Both these patients were in the anti-PR3 group. Four patients presented with intra-alveolar hemorrhage (three patients in the anti-PR3 group and one patient in the anti-MPO group). No neurological or digestive impairment was found in our study population. Initial renal involvement was almost always rapidly progressive glomerulonephritis. No case of nephrotic syndrome or macroscopic hematuria was identified. However, microscopic hematuria and proteinuria occurred in all patients. Four patients needed renal replacement therapy at the time of diagnosis.

The median creatinine at admission was 420 (205 - 647) µmol/L and the mean proteinuria was 0.84 g/day.

Table 1. Summary of the baseline patients' data.

	Case No. 1	Case No. 2	Case No. 3	Case No. 4	Case No. 5	Case No. 6
Age	73	46	80	43	56	68
Sex	F	M	F	M	F	M
Type of ANCA	Anti-PR3	Anti-DFO	Anti-DFO	Anti-PR3	Anti-PR3	Anti-PR3
BVAS	14	15	28	27	21	21
VDI	2	3	5	0	4	3
FFS	3	2	4	1	2	2
IAH	NO	NO	YES	YES	YES	YES
Dialysis dependency	NO	NO	NO	NO	YES	NO

ANCA: Anti-Neutrophil Cytoplasm Antibody; **BVAS**: Birmingham Vasculitis Activity Score; **VDI**: Vasculitis Damage Index; FFS: Five-Factor Score; **IAH**: Intra-Alveolar Hemorrhage.

Inflammatory syndrome was present in all the patients with an average CRP of 82 mg/L. All patients had positive ANCAs at diagnosis with the presence of anti-MPO specificity in two of six cases and specificity anti-PR3 in four of six cases.

The induction treatment consisted of a weekly course of rituximab at 375 mg/m^2 for one month (five of six cases) or two infusions of 1 g of rituximab 15 days apart (one of six cases) combined with intravenous (IV) boluses of methylprednisolone for 3 consecutive days at doses of 1 gram per day (five of six patients) or 500 mg/day (one of six patients): methylprednisolone was started immediately after the first plasmapheresis session. Plasmapheresis was given to all six patients (this had been part of the selection criteria) every other day. Four sessions were started before the first rituximab infusion; three days thereafter the other plasmapheresis sessions were performed followed by the second rituximab injection. The main indications for apheresis were alveolar hemorrhage (n = 4), severe renal insufficiency > 350 mmol/L (n = 1), and persistent worsening of renal failure despite conventional treatment with corticosteroids associated with rituximab (n = 1). The total number of plasmapheresis sessions given was six for two patients and seven sessions for four others. Substitution with fresh frozen plasma (FFP) instead of albumin was implemented in those who have had a recent renal biopsy and/or in the event there was alveolar hemorrhage. All patients were treated with rituximab for maintenance after a first attack or its recurrence. Outcomes were favorable for five patients. Only one patient became dependent on hemodialysis. There was no mortality. Among patients who recovered (n = 5) at last follow-up median proteinuria and median serum creatinine were respectively 0.5 g/day and 199 μmol/L. At the last follow-up, there was no relapse.

4. Discussion

Granulomatosis with polyangiitis and microscopic polyangiitis can be revealed from fever and/or deterioration in general condition and is present in most ANCA patients [5]. In accordance with published data, 50% of our patients presented with fever and/or deterioration of general condition.

Renal involvement during ANCA vasculitis is most often manifested by rapidly progressive glomerulonephritis (RPGN) associated with proteinuria that is usually greater than or equal to 1 g per 24 hours, plus hematuria. RPGN has been described in between 38% and 100% of patients, depending on the series [7] [8]. In our study, the totality of patients presented with RPGN. Average creatinine level at diagnosis was 417 mmol/L. No case of nephrotic syndrome or macroscopic hematuria occurred, although this has been sometimes described in ANCA vasculitis [8]. However, microscopic hematuria and proteinuria were evident in all of our patients.

In the cases of RPGN with or without pulmonary hemorrhage we have to address the value of having plasmapheresis as part of the very initial therapy. Recently Yamada *et al.* performed a systematic review and meta-analysis on the ef-

ficacy of plasma exchange for antineutrophil cytoplasmic antibody-associated systemic vasculitis: although performing plasmapheresis was not associated with the risk of mortality, complete response or adverse events, when focusing on the early treatment phases, plasmapheresis was associated with a reduction in end-stage renal disease incidence compared with both no plasmapheresis -PP- (PP 1/43 vs. no PP 10/41; RR 0.14 [0.03 - 0.77] at 3 months) and pulse steroid (PP 11/70 vs. pulse steroid 23/67; RR 0.46 [0.24 - 0.86] at 3 months) [9]. However, the PEXIVAS study has shown that among patients with severe ANCA-associated vasculitis, the use of plasma exchange did not reduce the incidence of death or end-stage kidney disease [10]. Nonetheless, in a subset of patients presenting with alveolar hemorrhage, there was a trend towards a better outcome of such cases receiving PP. This would be in line with observational studies reporting a recovery of alveolar hemorrhage following extracorporeal treatment [11]. This was recently challenged by Specks *et al.* regarding the usefulness of plasmapheresis at early stages of severe ANCA-associated vasculitis [12].

In our study, we used in addition to rituximab high doses of steroids. Recently the American College of Rheumatology conditionally recommended for patients with active, severe GPA/MPA, the treatment with rituximab over cyclophosphamide for remission induction. In addition, they recommended that for patients with active, severe GPA/MPA, either IV pulse glucocorticoids or high-dose oral glucocorticoids may be prescribed as part of initial therapy [13]. However, a recent study has shown that among patients with newly diagnosed ANCA-associated vasculitis without severe glomerulonephritis or alveolar hemorrhage, a reduced-dose glucocorticoid plus rituximab regimen was noninferior to a high-dose glucocorticoid plus rituximab regimen regarding induction of disease remission at 6 months [14].

How did we manage our patients? Our therapeutic management complied with accepted recommendations [15]. All patients received a combination of intravenous corticosteroids and rituximab as the induction treatment. This consisted of a weekly course of rituximab at 375 mg/m^2/week for one month (five of our six cases) or two infusions of 1 g of rituximab 15 days apart (one of our six cases), combined with intravenous (IV) boluses of methylprednisolone for 3 consecutive days at doses of 1 g/d (five of six patients) or 500 mg/d (one of six patient). Retrospective studies suggest comparable efficacy of this schedule with two infusions of 1 g of rituximab 15 days apart compared to 4 weekly injections, even though a schedule of two infusions has not been validated as induction treatment for ANCA-associated vasculitis [15].

The results from the RAVE and RITUXVAS studies report the effectivity of rituximab compared to cyclophosphamide [16] [17]. However, cyclophosphamide still has a place, particularly for certain indications [15]: e.g., the presence of associated anti-glomerular basement-membrane antibodies; severe alveolar hemorrhage that requires mechanical ventilation (patients excluded from the RAVE trial); rapidly progressive renal failure with serum creatinine > 350 mmol/L (patients excluded from the RAVE trial); failure or in-complete response to ri-

tuximab; and predominantly granulomatous forms (essentially tracheal and/or bronchial stenoses, impairments that threaten a functional or vital prognosis).

We made the choice to perform plasmapheresis because presented with severe renal insufficiency > 350 mmol/L with or without alveolar hemorrhage. The total number of apheresis sessions was six for two patients and seven sessions for the other four patients. Substitution with fresh frozen plasma has been indicated in the context of a recent renal biopsy and/or in the event of alveolar hemorrhage. Our results are similar to those of the protocol for the MEPEX study [18] where the average number of sessions was seven per patient, carried out over 15 days. However, in contrast, our patients received steroid boluses in association with plasma exchange.

In accordance with the recommendations, all patients have had high-dose oral cortico-steroids with subsequent tapering. The total duration of corticosteroid therapy varies from 5 - 6 months according to North American protocols, to 18 - 24 months for European protocols [15]. In France, a prednisone reduction schedule of ~20 mg/d at 3 months, to 10 mg/d at 6 months, and 5 mg/d at one year is suggested.

All our patients received rituximab for a first attack or for a recurrence. This approach is in line with the MAINRITSAN study, which concluded that rituximab had a clear clinical benefit over azathioprine as a maintenance treatment for ANCA vasculitis [19]. In addition, if there is a relapse, rituximab is significantly associated with a better remission rate than cyclophosphamide therapy [20], and thus should be preferred over cyclophosphamide to treat severe active forms in relapsed patients and for women of childbearing age.

In our study, three patients had relapses of AAV. No mortalities occurred. Only one patient became dependent on hemodialysis

5. Conclusion

In the setting of ANCA-associated vasculitis, apheresis may be beneficial at the very beginning of therapy, particularly for those that have a severe presentation, such as intra-alveolar hemorrhage.

Conflicts of Interest

The authors declare no conflicts of interest.

Informed Consent

Informed consent was obtained from all patients.

References

[1] Jennette, J.C., Falk, R.J., Bacon, P.A., Basu, N., Cid, M.C., Ferrario, F., Flores-Suarez, L.F., Gross, W.L., Guillevin, L., Hagen, E.C., Hoffman, G.S., Jayne, D.R., Kallenberg, C.G., Lamprecht, P., Langford, C.A., Luqmani, R.A., Mahr, A.D., Matteson, E.L., Merkel, P.A., Ozen, S., Pusey, C.D., Rasmussen, N., Rees, A.J., Scott, D.G., Specks, U., Stone, J.H., Takahashi, K. and Watts, R.A. (2013) 2012 Revised International

Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis & Rheumatology*, **65**, 1-11. https://doi.org/10.1002/art.37715

[2] Mahr, A., Guillevin, L., Poissonnet, M. and Ayme, S. (2004) Prevalences of Polyarteritis Nodosa, Microscopic Polyangiitis, Wegener's Granulomatosis, and Churg-Strauss Syndrome in a French Urban Multiethnic Population in 2000: A Capture-Recapture Estimate. *Arthritis & Rheumatology*, **51**, 92-99. https://doi.org/10.1002/art.20077

[3] Watts, R.A., Gonzalez-Gay, M.A., Lane, S.E., Garcia-Porrua, C., Bentham, G. and Scott, D.G. (2001) Geoepidemiology of Systemic vasculitis: Comparison of the Incidence in Two Regions of Europe. *Annals of the Rheumatic Diseases*, **60**, 170-172. https://doi.org/10.1136/ard.60.2.170

[4] Karras, A. (2019) Renal Involvement of Anti-Neutrophil Cytoplasm Antibody Vasculitis. *EMC-Nephrologie*, **16**, 1-10.

[5] Terrier, B. (2019) Treatment of Vasculitis at ANCA: Certainties and Controversies. *Néphrologie & Thérapeutique*, **15**, S7-S12. https://doi.org/10.1016/j.nephro.2019.02.008

[6] Mukhtyar, C., Guillevin, L., Cid, M.C., Dasgupta, B., de Groot, K., Gross, W., Hauser, T., Hellmich, B., Jayne, D., Kallenberg, C.G., Merkel, P.A., Raspe, H., Salvarani, C., Scott, D.G., Stegeman, C., Watts, R., Westman, K., Witter, J., Yazici, H. and Luqmani, R., for the European Vasculitis Study Group (2009) EULAR Recommendations for the Management of Primary Small and Medium Vessel Vasculitis. *Annals of the Rheumatic Diseases*, **68**, 310-317. https://doi.org/10.1136/ard.2008.088096

[7] Berti, A., Cornec, D., Crowson, C.S., Specks, U. and Matteson, E.L. (2017) The Epidemiology of Antineutrophil Cytoplasmic Autoantibody-Associated Vasculitis in Olmsted County, Minnesota. *Arthritis & Rheumatology*, **69**, 2338-2350. https://doi.org/10.1002/art.40313

[8] Puecha, X. (2007) Vasculitis Associated with Polymorphonuclear Anticytoplasm Antibodies.

[9] Yamada, Y., Harada, M., Hara, Y., Iwabuchi, R., Hashimoto, K., Yamamoto, S. and Kamijo, Y. (2021) Efficacy of Plasma Exchange for Antineutrophil Cytoplasmic Antibody-Associated Systemic Vasculitis: A Systematic Review and Meta-Analysis. *Arthritis Research & Therapy*, **23**, Article No. 28. https://doi.org/10.1186/s13075-021-02415-z

[10] Walsh, M., Merkel, P.A., Peh, C.A., Szpirt, W.M., Puéchal, X., Fujimoto, S., Hawley, C.M., Khalidi, N., Floßmann, O., Wald, R., Girard, L.P., Levin, A., Gregorini, G., Harper, L., Clark, W.F., Pagnoux, C., Specks, U., Smyth, L., Tesar, V., Ito-Ihara, T., de Zoysa, J.R., Szczeklik, W., Flores-Suárez, L.F., Carette, S., Guillevin, L., Pusey, C.D., Casian, A.L., Brezina, B., Mazzetti, A., McAlear, C.A., Broadhurst, E., Reidlinger, D., Mehta, S., Ives, N., Jayne, D.R.W., for the PEXIVAS Investigators (2020) Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis. *The New England Journal of Medicine*, **382**, 622-631. https://doi.org/10.1056/NEJMoa1803537

[11] Kronbichler, A., Shin, J.I., Wang, C.S., Szpirt, W.M., Segelmark, M., Tesar, V. (2021) Plasma Exchange in ANCA-Associated Vasculitis: The Pro Position. *Nephrology Dialysis Transplantation*, **36**, 227-231. https://doi.org/10.1093/ndt/gfaa311

[12] Specks, U., Fussner, L.A., Cartin-Ceba, R., Casal Moura, M., Zand, L., Fervenza, F.C. (2021) Plasma Exchange for the Management of ANCA-Associated Vasculitis: The Con Position. *Nephrology Dialysis Transplantation*, **36**, 231-236. https://doi.org/10.1093/ndt/gfaa312

[13] Chung, S.A., Langford, C.A., Maz, M., Abril, A., Gorelik, M., Guyatt, G., *et al*.

(2021) 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. *Arthritis Care & Research*, **73**, 1088-1105. https://doi.org/10.1002/acr.24634

[14] Furuta, S., Nakagomi, D., Kobayashi, Y., Abril, A., Gorelik, M., Guyatt, G., Archer, A.M., Conn, D.L., Full, K.A., Grayson, P.C., Ibarra, M.F., Imundo, L.F., Kim, S., Merkel, P.A., Rhee, R.L., Seo, P., Stone, J.H, Sule, S., Sundel, R.P., Vitobaldi, O.I., Warner, A., Byram, K., Dua, A.B., Husainat, N., James, K.E., Kalot, M.A., Lin, Y.C., Springer, J.M., Turgunbaev, M., Villa-Forte, A., Turner, A.S., Mustafa, R.A., for the LoVAS Collaborators (2021) Effect of Reduced-Dose vs High-Dose Glucocorticoids Added to Rituximab on Remission Induction in ANCA-Associated Vasculitis: A Randomized Clinical Trial. *JAMA*, **325**, 2178-2187. https://doi.org/10.1001/jama.2021.6615

[15] French Group for the Study of Vasculitis GFEV (2019) Update of the PNDS Systemic Necrotizing Vasculitis. https://www.vascularites.org

[16] Jones, R.B., Tervaert, J.W., Hauser, T. Luqmani, R., Morgan, M.D., Peh, C.A., Savage, C.O., Segelmark, M., Tesar, V., van Paassen, P., Walsh, D., Walsh, M., Westman, K. and Jayne, D.R., for the European Vasculitis Study Group (2010) Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis. *The New England Journal of Medicine*, **363**, 211-220. https://doi.org/10.1056/NEJMoa0909169

[17] Stone, J.H., Merkel, P.A., Seo, P. Langford, C.A., Hoffman, G.S., Kallenberg, C.G., St Clair, E.W., Turkiewicz, A., Tchao, N.K., Webber, L., Ding, L., Sejismundo, L.P., Mieras, K., Weitzenkamp, D., Ikle, D., Seyfert-Margolis, V., Mueller, M., Brunetta, P., Allen, N.B., Fervenza, F.C., Geetha, D., Keogh, K.A., Kissin, E.Y., Monach, P.A., Peikert, T., Stegeman, C., Ytterberg, S.R. and Specks, U. (2010) Rituximab versus Cyclophosphamide for Induction of Remission in ANCA-Associated Vasculitis: A Randomized Controlled Trial (RAVE). *The New England Journal of Medicine*, **363**, 221-232. https://doi.org/10.1056/NEJMoa0909905

[18] Jayne, D.R.W., Gaskin G., Rasmussen, N., Abramowicz, D., Ferrario, F., Guillevin, L., Mirapeix, E., Savage, C.O., Sinico, R.A., *et al*., for the European Vasculitis Study Group (2007) Randomized Trial of Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis. *Journal of the American Society of Nephrology*, **18**, 2180-2188. https://doi.org/10.1681/ASN.2007010090

[19] Guillevin, L., Charles, P., Karras, A., Khouatra, C., Aumaître, O., Cohen, P., *et al*., for the French Vasculitis Study Group (2014) Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis. *The New England Journal of Medicine*, **371**, 1771-1780. https://doi.org/10.1056/NEJMoa1404231

[20] Specks, U., Merkel, P.A., Seo, P., Spiera, R., Langford, C.A., Hoffman, G.S., *et al*., for the RAVE-ITN Research Group (2013) Efficacy of Remission-Induction Regimens for ANCA-Associated Vasculitis. *The New England Journal of Medicine*, **369**, 417-427. https://doi.org/10.1056/NEJMoa1213277