Saudi J Kidney Dis Transpl 2012;23(2):301-305

Saudi Journal of Kidney Diseases and Transplantation

Original Article

Clinical Features and Outcomes of ANCA-Associated Renal Vasculitis

Sidy Mohamed Seck[1], Bertrand Dussol[2], Philippe Brunet[2], Stephane Burtey[2]

[1]Nephrology Department, University Hospital Aristide, Le Dantec, Dakar, Senegal,
[2]Nephrology Department, University Hospital La Conception, Marseille, France

ABSTRACT. To determine the patterns and outcomes of the pauci-immune vasculitis in the nephrology department at hospital La Conception in Marseille, we conducted a retrospective study including all patients with diagnosis of pauci-immune renal vasculitis between January 1, 2000 and December 31, 2007. Among 33 cases, 25 were diagnosed as Wegener granulomatosis (WG), seven as microscopic polyangitis (MPA) and one as Churg-Strauss syndrome (SCS). The median age of the patients was 57.7 years and the sex-ratio (M/F) was 1.6. The visceral manifestations included kidneys (100% of patients), lungs (75%), ENT (52% of WG), and nervous system (57% of MPA). The mean serum creatinine at admission was 3.3 mg/dL. Renal biopsies revealed a pauci-immune crescentic gromerulonephritis in 96% of the cases. Two patients with WG received plasmapheresis and seven patients required emergency hemodialysis. Induction therapy comprised cyclophosphamide IV and corticosteroids, while maintenance therapy included azathioprine for the majority of patients. Eighty four percent of the patients experienced complete remission after induction therapy. During maintenance therapy relapses were more frequent among patients with MPA (28%) compared to WG cases (12%). After 35 months of follow-up, eight patients ended on chronic hemodialysis, and five patients died. ANCA associated vasculitis are frequent in our patients. Long-term outcomes are relatively good despite a mortality rate of 15% and 25% of the patients entering dialysis after three years of follow-up.

Introduction

Pauci-immune vasculitis associated with anti-neutrophil cytoplasmic antibodies (ANCA) are characterized by inflammation of small vessels (arterioles, venules and capillaries).[1] They comprise many diseases such as Wegener granulomatosis (WG), microscopic polyangitis (MPA), Churg and Strauss syndrome (CSS), and renal limited vasculitis. Kidney injury is frequent in ANCA vasculitis and represents a strong prognosis factor.[2,3]

The aim of this study was to determine the clinical and laboratory patterns and outcomes of patients with ANCA associated vasculitis at a referral center in France.

Correspondence to:

Dr. Sidy Mohamed Seck,
Nephrology Department,
University Hospital Aristide Le Dantec,
30 Avenue Pasteur, BP 3001 Dakar, Senegal
E-mail: sidymseck@gmail.com

Table 1. Clinical manifestations of ANCA-associated vasculitis including Wegener granulomatosis (WG) microscopic polyangitis (MPA), and Churg–Strauss syndrome (CSS).

Symptoms	WG	PMA	CSS
Pulmonary			
Hemoptysia	72%	1.4%	00%
Persistant dry cough	15%	50%	100%
Ear Nose &Throat			
Rhinitis	28%	20%	0%
Sinusitis	48%	0%	0%
Skin			
Vascular purpura	16%	8%	0%
Raynaud's syndrome	4%	0%	0%
High blood pressure	76%	79.4%	100%
Rheumatologic			
Peripheral arthritis	28%	71.4%	100%
Neurological			
Mono- or	8%	0%	0%
Polyneuropathy	32%	57%	0%
Gastro-intestinal			
Abdominal pain	12%	28%	0%
Others			
Fatigue	56%	57%	100%
Weight loss	60%	57%	100%

Patients and Methods

We conducted a retrospective observational study between January 1 and December 31, 2007 at the nephrology department in university hospital La Conception in Marseille, France. All patients with diagnosis of ANCA vasculitis and followed during this period were included. WG and SCS were diagnosed according to the ACR criteria.[4] Chapel Hill classification was used for diagnosis of MPA.[1] Severity of vasculitis was assessed with the Birmingham Vasculitis Assessment Score (BVAS)[5] and Five Factor Score (FFS).[6] Sociodemographic, clinical, and laboratory data were collected from medical records. Statistical analysis was done with Microsoft Excel 2007.

Results

Among 40 cases of ANCA vasculitis, we excluded seven patients because of incomplete data. Thirty-three patients were effectively included in the study and comprised 25 cases with Wegener granulomatosis (WG), seven with microscopic polyangitis (MPA) and one with Churg–Strauss syndrome (SCS). The median age of the patients was 57.7 years and the sex ratio (M/F) was 1.6. Prevalence of ANCA-associated vasculitis during the study period was 0.5 %. Pulmonary-renal syndrome was the most frequent cause of admission (62% of patients). The mean duration between the onset and diagnosis of vasculitis was 14 ± 3.2 weeks (01 – 42 weeks). Clinical and biological characteristics of patients are presented in Tables 1 and 2.

Renal biopsies were available in 28 cases and revealed pauci-immune crescentic glomerulonephritis in 96% of them. Tubulo-interstitial lesions were present in 46% of the cases. Histology did not reveal any granulomas even in WG. The mean BVAS and FFS prognosis scores were 41.7 (20-52), 1.78 (1–3) and 0, for patients with WG, MPA, and CSS, respectively.

Induction therapy consisted of corticosteroids (CTC) 1 mg/kg/day and 0.6 g/m^2 of IV cyclophosphamide (CYC) adapted to creatinine clearance of the patients. CTC was taken daily at and CYC was administered monthly for six months. After that CYC pulses were given every three months until one year; in two patients with

Table 2. Biological parameters at admission of patients.

Parameters	Value (mean ± standard deviation)		
	GW	PAM	SCS
Serum creatinine (mg/dL)	5.53 ± 0.8	5 ± 0.3	4.34
Creatinine clearance*(mL/mn)	11.4 ± 8	15.8 ± 28	18
Proteinuria (g/24 h)	1.7 ± 0.9	1.65 ± 1.4	1.2
Hematuria	56%	44%	100%
Leukocyturia	45%	32%	100%
Hemoglobin (g/dL)	8.5 ± 3	10.3 ± 6	11
Hypereosinophilia	4%	0%	100%
c-ANCA (againts PR3)	92%	0%	00%
p-ANCA (against MPO)	4%	100%	100%
Atypical p-ANCA	4%	0%	00%

*Estimated with Cockroft–Gault formula.
PR3: proteinase 3, MPO: myeloperoxydase.

WG, CYC was administrated by oral route at 2 mg/kg/day. Four cases of severe MPA, received three consecutive pulses of CTC (10 mg/kg/day) during the induction therapy. Two patients with WG and intra-alveolar hemorrhage underwent plasmapheresis (five sessions) and seven patients required acute emergency hemodialysis. For maintenance therapy, oral CTC (5–10 mg/day) was used in combination with azathioprine (100–150 mg/day) in 93.8% of the WG and MPA cases. Methotrexate (20 mg/week) replaced azathioprine (AZA) in two patients. The mean duration of maintenance therapy was 10.6 ± 6 months (eight to –25 months). The case of CSS was treated with CTC (1 mg/kg/day) during four weeks rapidly tapered to maintenance dose of 10 mg/day and then continued for 12 months.

After induction therapy, the remission rate was 80% and 86% for patients with WG and MPA, respectively. During the maintenance period, relapses occurred in 12% of MPA and 28% of the WG cases. Two cases of resistant WG were treated with rituximab (four injections of 375 mg/m^2) and stabilized their renal function. Evolution of patients' serum creatinine levels according to type of vasculitis is represented in figure 1.

The major complications included azathioprine-induced bone marrow toxicity (two cases), intercostal herpes zoster (one case) and severe sepsis (eight cases). The number of relapses was not significantly correlated with occurrence of end-stage renal disease (ESRD) (r=0.46, *P*=0.15). However, the presence of severe tubulo-interstitial injuries was more frequent in the dialysis-dependent patients. After a follow-up period of 35 months, eight patients with ESRD entered chronic hemodialysis without any relapse, and two patients were transplanted after 17 and 25 months; the grafts function was normal. Five patients died because of septicemia during the induction therapy.

Discussion

Prevalence of ANCA vasculitis in our study was lower than that reported in the general population.[3,7,8] This discrepancy relates to the fact that only patients with severe renal injury were included in our study. Most of the patients with ANCA-associated vasculitis were followed by specialists other than nephrologists. Compared to other studies, our patients were younger but male predominance was similar.[7] The clinical presentation was dominated by pulmonary-renal syndrome and ENT symptoms as reported by other authors.[3] Intestinal vasculitis found in two cases was associated with severe forms of vasculitis.[9] The immunological findings were very suggestive of the diagnosis in the majority of patients revealing anti-PR3 ANCA and anti-MPO ANCA, usually described in WG and MPA, respectively.[3,7] However, atypical ANCA are not rare and seem to be associated with a better prognosis.[10] Renal biopsies in ANCA-associated vasculitis classically show crescentic glomerulo-

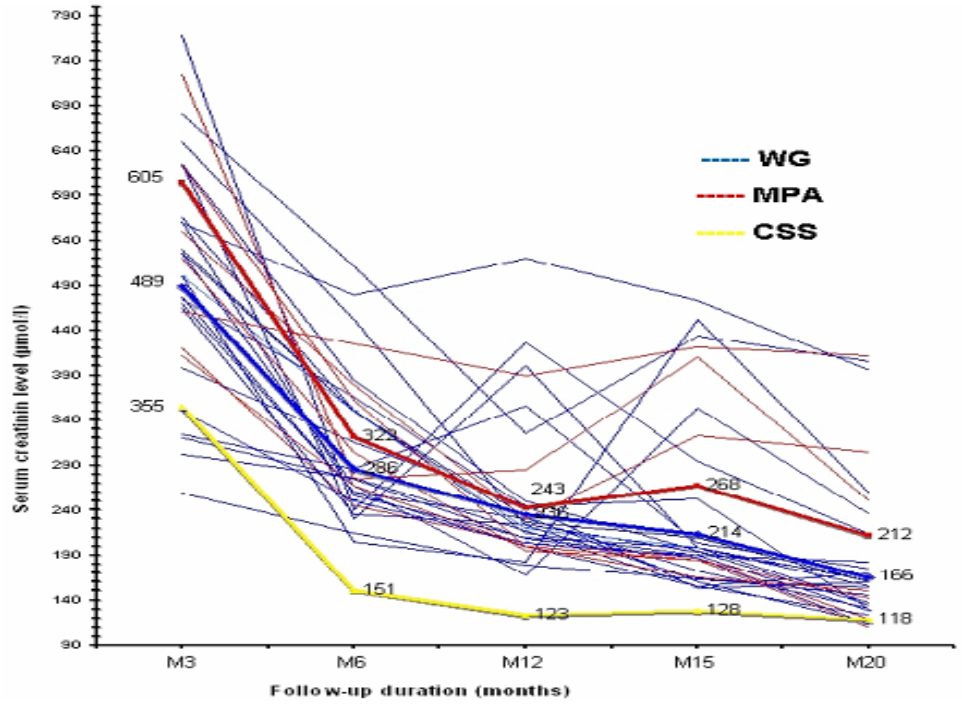

Figure 1. Evolution of serum creatinine during follow-up in our patients with the different vasculitis including Wegener granulomatosis (WG) microscopic polyangitis (MPA), and Churg-Strauss syndrome (CSS).

nephritis as found in the majority of our patients.[8,15] The tubulo-interstitial lesions were predominantly observed in WG and could explain largely the worse renal outcomes in these patients.[11]

The combination of CTC and CYC at induction phase followed by azathioprine was the most used therapeutic regimen and associated with high remission rate (80%) in our patients. This regimen is widely used in many centers.[3,8,12,13] CYC pulses are as efficient as oral route and well tolerated.[12] Methotrexate is equivalent to AZA for maintenance therapy but adverse effects are not lower.[14] Its prescription should be restricted to patients with localized form of WG and during maintenance period.[13,14] Plasma exchanges are currently recommended in patients with severe renal damages (serum creatinine $\geq$ 600 µmol/L).[13] Monoclonal anti-CD20 antibodies improved renal function in two cases of WG resistant to the usual drug therapy. Rituximab-induced remission was also reported in small-sized studies of patients with ANCA vasculitis resistant to CYC, but more randomized controlled trials are needed.[16] The remission rate and long-term survival in our study were lower than usually reported in other studies.[17-19] Twenty of our patients became dialysis independent after a 35-months follow-up. These bad outcomes are linked to bad prognosis scores (BVAS and FFS) in our patients, less aggressive induction therapy, and short duration of treatment in some of them. A minimal maintenance period of 18 months is generally required.[13] Mycophenolate mophetil may be safe and efficient for maintenance therapy.[19] Better prognosis in patients with MPA and SCS compared to WG was already noticed in previous studies.[8,17,19]

After remission, monitoring of ANCA titers was used for early detection of relapses. However, the predictive value of ANCA antibodies is not well demonstrated and increased level should not justify escalation of therapy.[8,20] High mortality rate in our study was compatible with previous studies which reported an important number of deaths during first year of

treatment.[18,21,22] In a large retrospective study by Slot et al, dialysis need at diagnosis was identified as a major risk factor of death during the first year.[23] However, the first year mortality rate in our patients was much lower than in other studies.[19,23]

References

1. Jennette JC, Falk RJ, Andrassy K, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum 1994;37:187-92.
2. Gayraud M, Guillevin L, Le Toumelin P, et al. Long-term follow-up of polyarteritis nodosa, microscopic polyangitis and Churg-Strauss syndrome: Analysis of four prospective trials including 278 patients. Arthritis Rheum 2001; 44:666-75.
3. Pagnoux C. Wegener's granulomatosis and microscopic polyangitis. Rev Prat 2008;58(5): 522-32.
4. Leavitt RY, Fauci AS, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum 1990;33(8): 1101-7.
5. Luqmani RA, Bacon PA, Moots RJ, et al. Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. Q J Med 1994;87:671-8.
6. Guillevin L, Lhote F, Gayraud M, et al. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. Medicine (Baltimore) 1996;75(1):17-28.
7. Watts RA, Scott DG. Epidemiology of the vasculitides. Semin Respir Crit Care Med 2004; 25:455-64.
8. Puéchal X. Antineutrophil cytoplasmic antibody-associated vasculitis. Rev Rhum 2007;74:824-32.
9. Pagnoux C, Mahr A, Guillevin L. Abdominal and digestive manifestations in systemic vasculitides. Ann Med Intern 2003;154(7):457-67.
10. Drooger JC, Dees A, Swaak AJ. ANCA-positive patients: the influence of PR3 and MPO Antibodies on survival rate and the association with clinical and laboratory characteristics. Open Rheumatol J 2009;3:14-7.
11. Son D, Kanda H, Yamaguchi A, et al. Myeloperoxidase antineutrophil cytoplasmic antibody-associated vasculitis with diffuse tubulointerstitial nephritis. J Nephrol 2009;22(3):417-20.
12. de Groot K, Harper L, Jayne DR, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med 2009;150(10): 670-80.
13. Pagnoux C, Mahr A, Hamidou MA, et al. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. N Engl J Med 2008; 359(26):2790-803.
14. Nachman PH. Vasculitis syndromes: which maintenance therapy for ANCA vasculitis? Nat Rev Nephrol 2009;5(5):254-6.
15. Savage CO, Winearls CG, Evans DJ, Rees AJ, Lockwood CM. Microscopic polyarteritis: presentation, pathology and prognosis. Q J Med 1985;56:467-83.
16. Pallan L, Savage CO, Harper L. ANCA-associated vasculitis: from bench research to novel treatments. Nat Rev Nephrol 2009;5(5):278-86.
17. Westman KW, Bygren PG, Olsson H, Ranstam J, Wieslander J. Relapse rate, renal survival, and cancer morbidity in patients with Wegener's granulomatosis or microscopic polyangiitis with renal involvement. J Am Soc Nephrol 1998;9 (5):842-52.
18. Booth AD, Almond MK, Burns A, et al. Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. Am J Kidney Dis 2003;41 (4):776-84.
19. Iatrou C, Zerbala S, Revela I, et al. Mycophenolate mofetil as maintenance therapy in patients with vasculitis and renal involvement. Clin Nephrol 2009;72(1):31-7.
20. Lin W, Chen M, Zhao MH. Follow-up of avidity and titer of anti-myeloperoxidase antibodies in sera from patients with primary ANCA-associated vasculitis. Autoimmunity 2009;42 (3):198-202.
21. Little MA, Nightingale P, Verburgh CA, et al. Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis. Ann Rheum Dis 2010;69(6):1036-43.
22. Oh JS, Lee CK, Kim YG, Nah SS, Moon HB, Yoo B. Clinical features and outcomes of microscopic polyangiitis in Korea. J Korean Med Sci 2009;24(2):269-74.
23. Slot MC, Tervaert JW, Franssen CF, Stegeman CA. Renal survival and prognostic factors in patients with PR3-ANCA associated vasculitis with renal involvement. Kidney Int 2003;63 (2):670-7.