Editorial

Outcome in Small-Vessel Systemic Vasculitis


There are many questions to address in our current understanding of the natural history of systemic vasculitis. What is the outcome of small vessel systemic vasculitis as a result of current management? In other words, how effective are our current therapies in influencing the likely disease morbidity and mortality? Patients with primary small-vessel antineutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitis (AASV) have a potentially life-threatening disease. As a result of the introduction of chemotherapy, particularly cyclophosphamide, their outcome has been transformed from a mortality of 80% at one year[1] to survival of 55% in microscopic polyangiitis (MPA) and 75% in Wegener's granulomatosis (WG) at 10 years[2]. The subsequent disease course is unsatisfactory for most patients, due to low-grade grumbling disease, relapse, and the added effects of damage due to established disease or drug toxicity[2-5]. As a result, the burden of disease remains considerable in this group of survivors, so that their quality of survival is very inadequate and has driven the search to improve our current therapeutic strategies in vasculitis.

Although most patients with vasculitis survive their initial illness, late diagnosis remains a problem; patients may present with vague nonspecific features at an early stage of disease, and a diagnosis may be missed. Even after a diagnosis, delays in starting therapy can contribute to mortality if the disease is very active, with a timescale of days from initial presentation to end-organ failure in extreme cases[6].

Are there risk factors that would predict a worse outcome and for which we should take different management decisions? Guillevin and colleagues have proposed a 5-factor score based on the presence of raised serum creatinine, proteinuria, cardiac involvement, central nervous system involvement, or gut involvement[7]. Having any one of these 5 factors adversely affects the outcome of patients with Churg-Strauss syndrome (CSS) and polyarteritis nodosa (PAN). The 5-factor score has not been validated in other diseases such as WG or MPA. Assessment of disease activity can be standardized using clinical measures such as the introduction of the Birmingham Vasculitis Activity Score[8]. Disease damage can be evaluated in a systematic way, applying the Vasculitis Damage Index[4]. These clinical tools provide an accurate description of the current status of an individual patient; but more than this, they provide an opportunity to compare groups of patients in a standardized way.

In a new study by Pavone, *et al* reported in this issue of *The Journal*[9], 75 patients with primary systemic vasculitis have been evaluated for longterm prognosis and risk factors for poor outcome. There are organ-specific differences in rates of relapse. Gastrointestinal involvement in patients with CSS is associated with a high rate of relapse. By contrast, the presence of renal disease and the presence of a perinuclear-ANCA has a negative relationship with relapse; in other words these patients are less likely to relapse. A new finding is of an increased risk of relapse in Churg-Strauss patients with *Staphyloccocus aureus* nasal carriage; by contrast, the relapse risk is reduced in patients with WG who also carry *S. aureus*. These findings are difficult to explain when compared to previous evidence demonstrating a potential role for *S. aureus* and its toxins in exacerbating WG, and a 6-fold increase in relapse risk in patients with WG who are nasal carriers of *S. aureus* compared to those who are not. The authors suggest that these differences may be explained by the routine prescription of cotrimoxazole for all patients with WG, therefore artificially reducing the number of patients carrying *S. aureus*, or having a direct effect on the disease itself[10]. Interestingly, there was no influence of type of vasculitis on survival in this cohort. Clinical presentation may predict future outcome, at least in the first year of disease[8,11]. The Pavone study suggests that in CSS, patients have an increased risk of relapse if there is gastrointestinal involvement, supporting the concept that some clinical features can predict outcome[7,8,11-13].

See Outcome and prognostic factors during the course of primary small-vessel vasculitides, *page 1299*

Table 1. Mortality in prospective and selected retrospective outcome studies in PSV.

Study	Disease (No.)	Mortality Risk Factors	1 yr Survival	5 yr Survival
Pavone 2006[9]	PSV (75)	Age HR 4.05 Renal involvement HR 5.16 Hepatic involvement HR 4.29 ESR >100 HR 4.12 sCrea ≥132 HR 6.02	NA	78%
Lane 2005[18]	PSV (99) CSS,MPA,WG	NA	NA	MPA 45.1% WG 75.9% CSS 68.1%
Bligny 2004[19]	WG (93)	Age > 52 years RR 3.4 Absence of ENT RR 3.2	NA	WG 74%
Little 2004[20]	Renal SVV (86) WG (31), MPA (33) RLV (17)	Karnofsky score at diagnosis Treatment (worse with less aggressive) Diagnosis	85.5%	63%
Weidner 2004[21]	renal AAV (80) WG(32), MPA (28), RLV (20)	PR3 higher than MPO RR 9.32 Initial HD requirement Age >67 vs <56 RR 8.42 Crea>582 vs Crea<299 RR5.18	86%	81%
Slot 2003[22]	PR3 renal AAV (85)	Age 1 year increase RR 1.1 Mortality up to 1year HD at diagnosis RR 3.6 CRP 1mg/dl increase RR 1.01 Mortality > 1 year Male sex RR 5.75 HD dependency RR 4.15	80%	73%
Booth 2003[5]	renal PSV (264) MPA (120), WG(82), RLV (33), CSS (11)	Age>60 years Development of ESRF Crea>200 at diagnosis Sepsis	82%	76%
Mahr 2001[23]	WG (49)	SCrea> 18.1 RR 3.5 Age>57 RR 3.6	77.5% (6mo)	67.5% (2 years)
Gayraud 2001[11]	PSV (278) CSS(64), MPA(58), PAN(93), PAN HB(63)	Disease severity (BVAS,FFS) CSS with FFS>1 treated without CYC	NA	NA
Reinhold-Keller 2000[12]	WG (155)	Age > 50 RR 5.45 Nephritis (normal Crea) RR 2.41 Kidney failure RR 5.42 Lung involvement RR 3.75	99%	Median survival 21.7 years 88% (10 year)
Guillevin 1999[24]	MPA (85)	Proteinuria > 1g/d FFS superior to BVAS prognostically	NA	74%
Exley 1997[4]	SSV (120)	VDI at 2 year RR 8		
Hogan 1996[25]	MPA (107) RLV (38)	Pulmonary haemorrhage RR 8.65 cANCA vs pANCA RR 3.78 CS vs CYC/CS RR 5.56	NA	NA
Guillevin 1996[26]	324 PAN (260), CSS (82)	Proteinuria>1g/d RR3.6 Crea>1.58 RR 1.86 GI sx RR 2.83 Cardiomyopathy RR 2.18 CNS RR 1.76	NA	FFS=0 88.9% FFS=1 74.1% FFS>2 55 %
Gordon 1993[2]	idiopathic necrotizing vasculitis (150) PAN(12), MPA(95), WG (28), LWG (15)	NA	NA	100% PAN, LWG 55% MPA 75% WG (10year)
Hoffman 1992[3]	WG (158)	NA	NA	80%over study period
Guillevin 1988[7]	PAN+CSS (165)	Age>50 Gastrointestinal problems Cardiomyopathy Renal involvement	92%	63%

PSV: primary small-vessel vasculitis; CSS: Churg-Strauss syndrome; MPA: microscopic polyangiitis; WG: Wegener's granulomatosis; RLV: renal-limited vasculitis; renal AAV: ANCA associated vasculitis; sCREA: serum creatinine; MPO: myeloperoxidase; PR3: proteinase 3; ESRF: endstage renal failure; BVAS: Birmingham Vasculitis Activity Score; FFS: 5-factor score; CYC: cyclophosphamide; VDI: Vasculitis Damage Index; HB PAN: hepatitis B-associated polyarteritis nodosa; LWG: limited Wegener's granulomatosis.

The outcome in MPA differs from that of WG[2]. The mortality in patients with MPA is higher than in WG. However, the mortality rate in MPA is highest in the first year after diagnosis. By contrast, there is progressive mortality associated with WG over a number of years, perhaps reflecting the nature of the underlying disease process. In addition, the relapse rate in WG is higher than in MPA[14].

We have summarized the outcome of therapy from vasculitis in Tables 1 and 2, examining all large randomized prospective and selected retrospective studies of AASV with a minimum of one year followup. We have put the Pavone study into the tables for comparison with other large cohort studies of vasculitis.

The underlying pathogenesis of the systemic vasculitides is becoming better understood. Differences in the pathomechanisms may explain some of the variation in disease characteristics[15]. Why should organ-specific manifestations herald a risk of general relapse? Are there specific features in that organ that are critical to the relapse, or are they simply organs where subclinical disease can evolve into clinically overt manifestations at an earlier stage into recognizable symptoms, signs, or serological evidence of active vasculitis? For example, it is easier to detect a recurrence of skin vasculitis, manifesting as a rash, than to detect the presence of glomerulonephritis, which may only be found by careful testing of urine, assessment of renal function, and regular monitoring of blood pressure. Alternatively, some organs might be more prone to flares due to a higher likelihood of infection. Nasal colonization with *S. aureus* is, for example, associated with an increased risk of relapse of WG[10]. The pattern of organ involvement in a number of vasculitides is quite specific, even though in theory all vascular beds could be affected. Vascular flow, trauma, different vessel characteristics, and external agents such as infection or toxins may all influence the specific disease phenotype[15].

It is unlikely that our current therapies for systemic vasculitis will result in long-lasting drug-free remission or cure in the majority of cases. The quality of survival for most patients is unsatisfactory[2-5]. Measuring the morbidity of patients with vasculitis is an important advance in our ability to compare the effectiveness of different treatment regimens[4,8].

Controlled trials in systemic vasculitis are testing the effectiveness of different protocols utilizing existing drugs to their best ability to improve disease control while at the same time limiting toxicity[14,16]. Cyclophosphamide use can be limited to a comparatively short initial treatment at presentation or relapse[14], followed by a switch to azathioprine as a maintenance therapy. In limited forms of AASV without vital organ involvement, methotrexate could be used as a

Table 2. Relapse in prospective studies and selected retrospective outcome studies. For definitions see Table 1.

Study (Author/yr)	Disease	Relapse Risk Factors	Rate % /Duration of Followup	Time to Relapse
Pavone 2006[9]	PSV (75)	Gut involvement HR 3.26	1year 18% 2 years 27% 5 years 44%	Median 73 mo
Hogan 2005[17]	350 renal AAV	PR3 vs MPO RR 1.87 Lung or ENT involvement RR 1.7	No RF 26% / median 49mo 3 RF 47% / median 49mo	No RF median 62mo 3 RF median 39 mo
Weidner 2004[21]	80 renal AAV	No difference according to diagnosis or ANCA	33% / median 46.7 mo	Median 17.2 mo
Slot 2004[28]	128 AAV	ANCA pos at time of switch to AZA RR2.6 (for cANCA)	4 year 2year CYC/AZA(3m) 24% 49% CYC alone 24% 35% ANCA at AZA 42% 83%	NA
Bligny 2004[19]	93 WG	NA	45% / mean 4.5 years	Median 20 months
Little 2004[20]	86 Renal SVV	None significant	19% / mean 3.4 years	Rate of 0.08/patient year
Jayne 2003[14]	155 AAV		MPA 8%/ 18 months WG 18%/ 18 months	
Booth 2003[5]	264 renal PSV	WG PR 3	34%	Median 13months
Slot 2003[22]	PR3 renal AAV (85)	(all relapsing patients PR3 positive at time of relapse)	61% total 15 % only non-renal/ 46% renal /	Non renal median 3.3years Renal median 4.3 years
Mahr 2001[23]	WG (49)	na	43% / mean 1.9 years	mean 16mo
Gayraud 2001[11]	PSV 278	Diagnosis (no difference between CS or CS/CYC)	Total 20.1% / mean 88.3 mo HB PAN 7.9% / mean 88.3 mo PAN 19.4% / mean 88.3 mo CSS 20.3% / mean 88.3 mo MPA 34.5% / mean 88.3 mo	Total mean 31.6 mo HB PAN mean 36.6 mo PAN mean 29.4 mo CSS mean 24.6 mo MPA mean 37 mo
Reinhold-Keller 2000[12]	WG (155)	Longer followup	64% 13% up to 5 years, 71% more than 5 years	NA
Guillevin 1999[24]	85 MPA	NA	34.1% / mean 69.9 mo	mean 42.9months
Gordon 1993[2]	150 PSV	Nil significant	33.8% LWG 52.3%/ median24 mo PAN 41.7%/ median 54 mo WG 44%/ median 36 mo MPA 25.4%/ median 29 mo	 Median 18 mo Median 33mo Median 42mo Median 24mo
Hoffman 1992[3]	158 WG		49%/ mean 8years	NA

substitute for cyclophosphamide[16]. Conventional strategies with cyclophosphamide and steroid are being challenged by the increasing use of biologic agents. Thus far the evidence for disease control is disappointing for etanercept[17], but there may be a better response to other biologic agents.

RAASHID A. LUQMANI, DM, FRCP, FRCPE,
Consultant Rheumatologist,
Rheumatology Department,
Nuffield Orthopaedic Centre;
Senior Lecturer in Rheumatology,
Botnar Research Centre,
University of Oxford;
OLIVER FLOSSMANN, MRCP (UK),
EULAR Research Fellow in Vasculitis,
Botnar Research Centre,
Nuffield Orthopaedic Centre,
University of Oxford, Oxford, UK.

Address reprint requests to Dr. R.A. Luqmani, Rheumatology Department, Nuffield Orthopaedic Centre, Oxford OX3 7LD, UK. E-mail: raashid.luqmani@ndos.ox.ac.uk

REFERENCES

1. Walton EW. Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis). BMJ 1958;34:265-70.
2. Gordon M, Luqmani RA, Adu D, et al. Relapses in patients with a systemic vasculitis. Q J Med 1993;86:779-89.
3. Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med 1992;116:488-98.
4. Exley AR, Carruthers DM, Luqmani RA, et al. Damage occurs early in systemic vasculitis and is an index of outcome. Q J Med 1997;90:391-9.
5. Booth AD, Almond MK, Burns A, et al. Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. Am J Kidney Dis 2003;41:776-84.
6. Adu D, Howie AJ, Scott DG, Bacon PA, McGonigle RJ, Micheal J. Polyarteritis and the kidney. Q J Med 1987;62:221-37.
7. Guillevin L, Le Thi Huong D, Godeau P, Jais P, Wechsler B. Clinical findings and prognosis of polyarteritis nodosa and Churg-Strauss angiitis: a study in 165 patients. Br J Rheumatol 1988;27:258-64.
8. Luqmani RA, Bacon PA, Moots RJ, et al. Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. Q J Med 1994;87:671-8.
9. Pavone L, Grasselli C, Chierici E, et al. Outcome and prognostic factors during the course of primary small-vessel vasculitides. J Rheumatol 2006;33:1299-306.
10. Stegeman CA, Tervaert JW, de Jong PE, Kallenberg CG. Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. Dutch Co-Trimoxazole Wegener Study Group. N Engl J Med 1996;335:16-20.
11. Gayraud M, Guillevin L, le Toumelin P, et al. Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: analysis of four prospective trials including 278 patients. Arthritis Rheum 2001;44:666-75.
12. Reinhold-Keller E, Beuge N, Latza U, et al. An interdisciplinary approach to the care of patients with Wegener's granulomatosis: long-term outcome in 155 patients. Arthritis Rheum 2000; 43:1021-32.
13. Exley AR, Bacon PA, Luqmani RA, Kitas GD, Carruthers DM, Moots R. Examination of disease severity in systemic vasculitis from the novel perspective of damage using the vasculitis damage index (VDI). Br J Rheumatol 1998;37:57-63.
14. Jayne D, Rasmussen N, Andrassy K, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 2003;349:36-44.
15. Morgan MD, Harper L, Williams J, Savage C. Anti-neutrophil cytoplasm-associated glomerulonephritis. J Am Soc Nephrol 2006;17:1224-34.
16. de Groot K, Rasmussen N, Bacon PA, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2005;52:2461-9.
17. Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. N Engl J Med 2005;352:351-61.
18. Lane SE, Watts RA, Shepstone L, Scott DG. Primary systemic vasculitis: clinical features and mortality. Q J Med 2005;98:97-111.
19. Bligny D, Mahr A, Toumelin PL, Mouthon L, Guillevin L. Predicting mortality in systemic Wegener's granulomatosis: a survival analysis based on 93 patients. Arthritis Rheum 2004; 51:83-91.
20. Little MA, Nazar L, Farrington K. Outcome in glomerulonephritis due to systemic small vessel vasculitis: effect of functional status and non-vasculitic co-morbidity. Nephrol Dial Transplant 2004;19:356-64.
21. Weidner S, Geuss S, Hafezi-Rachti S, Wonka A, Rupprecht HD. ANCA-associated vasculitis with renal involvement: an outcome analysis. Nephrol Dial Transplant 2004;19:1403-11.
22. 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;63:670-7.
23. Mahr A, Girard T, Agher R, Guillevin L. Analysis of factors predictive of survival based on 49 patients with systemic Wegener's granulomatosis and prospective follow-up. Rheumatology Oxford 2001;40:492-8.
24. Guillevin L, Durand-Gasselin B, Cevallos R, et al. Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. Arthritis Rheum 1999;42:421-30.
25. Hogan SL, Nachman PH, Wilkman AS, Jennette JC, Falk RJ. Prognostic markers in patients with antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. J Am Soc Nephrol 1996;7:23-32.
26. 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;75:17-28.
27. Hogan SL, Falk RJ, Chin H, et al. Predictors of relapse and treatment resistance in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis. Ann Intern Med 2005;143:621-31.
28. Slot MC, Tervaert JW, Boomsma MM, Stegeman CA. Positive classic antineutrophil cytoplasmic antibody (C-ANCA) titer at switch to azathioprine therapy associated with relapse in proteinase 3-related vasculitis. Arthritis Rheum 2004;51:269-73.