

Small-Vessel and Medium-Vessel Vasculitis

PHILIP SEO¹ AND JOHN H. STONE²

Introduction

The vasculitides include a broad spectrum of disorders that span a clinical spectrum from benign, self-limited disease to fulminant conditions that are fatal in the absence of therapy. Whereas the large-vessel vasculitides consist of 2 principal disorders, giant cell arteritis and Takayasu arteritis, the medium- and small-vessel vasculitides are much more diverse, including multiple diseases that can affect nearly every organ system. This article is the second of a 2-part series that focuses on the challenges faced by clinicians who care for patients with vasculitis. The first article in this series discussed the large-vessel vasculitides (1). The present article will examine the medium- and small-vessel vasculitides, reviewing the recent literature for insights regarding their epidemiology, pathogenesis, and treatment.

Epidemiology

Is systemic vasculitis becoming more common? Recently, several reports have suggested that vasculitis is becoming more common (2,3). Whether these reports simply reflect an increased rate of recognition by clinicians is unclear (4). Watts et al (5) addressed this question by examining the incidence of the antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) in Norfolk, England, a demographically stable population of 430,000 adults. Data were collected prospectively between 1989 and 2003 at the Norfolk and Norwich University Hospital, the only referral center within this geographic area (6). The overall annual incidence of systemic vasculitis in this population was 19.9 cases per million (95% confidence interval [95% CI] 15.6–24.9). The incidence during the first 5-year period examined (1989–1993) was

20.3 cases per million (95% CI 14.6–27.2), and the incidence during the last 5-year period examined (1999–2003) was 17.1 cases per million (95% CI 12.1–23.5). Although the investigators did note a steady decline in the incidence of rheumatoid vasculitis, no significant changes in the incidence of Wegener's granulomatosis (WG), Churg-Strauss syndrome (CSS), or microscopic polyangiitis (MPA) were observed over the studied 15-year period.

A second study, conducted in northern Germany, reached similar conclusions. Reinhold-Keller et al (7) prospectively investigated a population of 2.8 million individuals for 5 years for new diagnoses of primary systemic vasculitis, including AAV. In that study, 642 incident cases of primary systemic vasculitis yielded an overall incidence of 54 cases per million (95% CI 39–68), somewhat higher than the incidence reported from Norwich (7). In 1999, the reported incidence of primary systemic vasculitis was 48 cases per million (95% CI 34–61). In 2002 (the final year of observation), the incidence had decreased to 42 cases per million (95% CI 31–52).

Both the British study and the German study were population based and relied on similar assumptions regarding population stability. Both capitalized on patterns of health care utilization that permitted the capture of the majority of relevant cases. Data from both groups supported the thesis that the incidence of primary systemic vasculitis has not increased during the recent past. In fact, both studies demonstrated a slight (albeit not significant) decrease in the incidence of systemic vasculitis over the periods studied.

Does rheumatoid vasculitis still exist? Over the past decade, the treatment paradigm for rheumatoid arthritis (RA) has favored early, aggressive therapy using potent immunomodulatory drugs to prevent joint destruction (8). This new paradigm has led to the hope that the most severe RA manifestations, particularly rheumatoid vasculitis, might in time disappear altogether (9). Two different groups have examined this question recently, reaching disparate conclusions.

As part of the Rochester Epidemiology Project, Turesson et al (10) analyzed all incident cases of RA (n = 609) in Olmsted County, Minnesota, from 1955 to 1994. Overall, 20 (3.1%) of the identified patients with RA developed rheumatoid vasculitis, defined as major cutaneous vasculitis or vasculitis-related neuropathy. The cumulative 10-year incidence rate for rheumatoid vasculitis was 2.1%

Supported by the NIH (National Institute of Arthritis and Musculoskeletal and Skin Diseases grant K23-AR-052820). Dr. Seo is a Lowe Family Scholar in the Center for Innovative Medicine at Johns Hopkins Bayview Medical Center.

¹Philip Seo, MD: Johns Hopkins University and The Johns Hopkins Vasculitis Center, Baltimore, Maryland; ²John H. Stone, MD, MPH: UpToDate, Waltham, Massachusetts.

Address correspondence to John H. Stone, MD, MPH, Rheumatic Diseases Unit, Massachusetts General Hospital, 55 Fruit Street, Yawkey 2C, Boston, MA 02114. E-mail: jhstone@partners.org.

Submitted for publication May 5, 2005; accepted in revised form May 22, 2007.

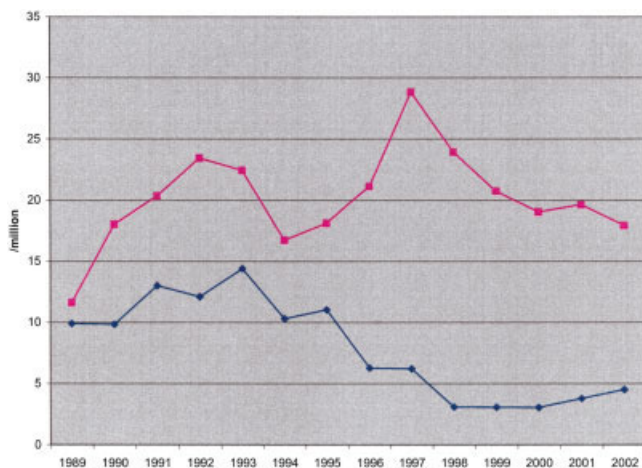


Figure 1. Incidence of both rheumatoid vasculitis and primary systemic vasculitis in England, 1989–2002, plotted as a rolling 3-year average. Blue diamonds = systemic rheumatoid vasculitis; pink squares = primary systemic vasculitis. Reproduced, with permission, from reference 11.

during the first decade (1955–1964) and 4.3% in the last decade studied (1985–1994), but the difference between these figures was not statistically significant ($P = 0.72$).

In another study, Watts et al (11) analyzed all incident cases of rheumatoid vasculitis in Norwich, England, between 1988 and 2002. A total of 51 cases were identified during this period, for an overall annual incidence of 7.9 cases per million. During the first 5-year period examined (1988–1992), the mean annual incidence was 11.6 cases per million. In contrast, during the last 5 years examined (1998–2002), the mean annual incidence declined to 3.6 cases per million (Figure 1).

Methodologic differences make these 2 studies difficult

to compare directly. The Rochester Epidemiology Project represents a population of 124,000 subjects with >40 years of followup. The prospective registry maintained by the Norfolk and Norwich University Hospital represents a population of >400,000 subjects but has existed only since 1988, and may have less complete data capture than the Rochester cohort. Unfortunately, neither study captured the full potential impact of tumor necrosis factor (TNF) inhibitors on the epidemiology of rheumatoid vasculitis.

Pathogenesis

Do leukotriene inhibitors cause Churg-Strauss syndrome? In 1998, Wechsler et al (12) reported a case series of 8 patients with glucocorticoid-dependent asthma who had been treated with zafirlukast, and subsequently developed a syndrome characterized by eosinophilia, pulmonary infiltrates, and cardiomyopathy consistent with CSS (Figure 2). Numerous subsequent reports have linked the use of leukotriene inhibitors with the onset of CSS (13), leading many clinicians to believe that the use of leukotriene antagonists is contraindicated in patients with this diagnosis.

This hypothesis was examined by Keogh and Specks (14), who reviewed 91 patients with CSS treated at the Mayo Clinic. Of these patients, 23 had received leukotriene receptor antagonists: 16 prior to diagnosis and 6 during clinical remission. The median interval between the onset of asthma and the development of vasculitis (4 years) did not differ according to leukotriene antagonist exposure history. Of the 6 patients with known CSS diagnoses, 4 remained in remission despite the use of leukotriene receptor antagonists. The other 2 patients experienced relapses during glucocorticoid tapers.

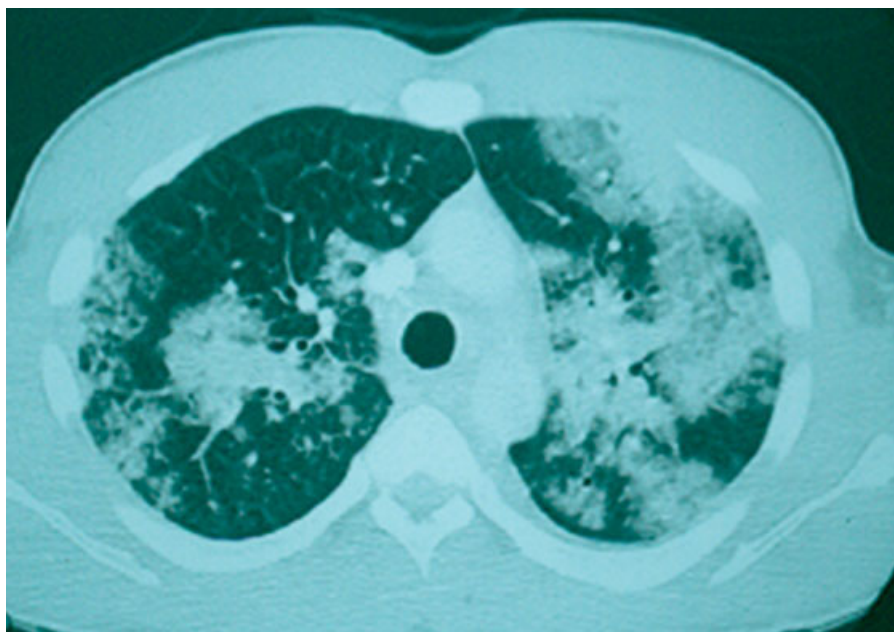


Figure 2. Pulmonary infiltrates in a patient with Churg-Strauss syndrome (CSS). This patient was negative for antineutrophil cytoplasmic antibodies (ANCA), consistent with a study indicating that patients with CSS who are ANCA negative have a higher likelihood of parenchymal lung disease and cardiac involvement, but a lower risk of vasculitic neuropathy.

Table 1. Demographics and clinical symptoms of Churg-Strauss syndrome in 112 patients according to their ANCA status (univariate analysis)*

Parameter	ANCA positive (n = 43)	ANCA negative (n = 69)	All patients (n = 112)	P (univariate analysis)
Lung	43 (100)	69 (100)	112 (100)	1
Asthma	43 (100)	69 (100)	112 (100)	1
Migratory lung infiltrates	24 (55.8)	49 (71.0)	73 (65.2)	0.10
Pleural effusion	3 (7)	22 (31.9)	25 (22.3)	0.002
Alveolar hemorrhage	3 (7)	5 (7.2)	8 (7.1)	0.96
Neurologic symptoms	36 (83.7)	46 (66.7)	82 (73.2)	0.048
Peripheral neuropathy	36 (83.7)	45 (65.2)	81 (72.3)	0.03
Central nervous system	5 (11.62)	5 (7.2)	10 (8.9)	0.43
Cardiac manifestations	5 (11.6)	34 (49.3)	39 (34.8)	< 0.0001
Pericarditis	3 (7)	25 (36.2)	28 (25)	0.0005
Cardiomyopathy	4 (9.3)	23 (33.3)	27 (24.1)	0.004
Renal manifestations	15 (34.9)	3 (4.3)	18 (16.1)	< 0.0001
Glomerulonephritis (biopsy proven)	8 (18.6)	0 (0)	8 (7.1)	0.0002
Creatininemia, mean \pm SD mg/dl	1.07 \pm 0.52	0.97 \pm 0.32	1 \pm 0.41	

* Values are the number (percentage) unless otherwise indicated. ANCA = antineutrophil cytoplasmic antibody. Reproduced, with permission, from ref. 18.

Although case reports of CSS associated with leukotriene inhibitors in the absence of glucocorticoid tapers continue to appear in the literature (15), these appear to represent exceptions to the rule. The data currently available imply that withholding leukotriene antagonists from patients with CSS is not warranted.

What is the significance of ANCA among patients with CSS? Although CSS is often considered to be an ANCA-associated form of vasculitis, a substantial percentage of patients with this disease are ANCA negative (16). This raises the question of whether patients with CSS who are ANCA positive are phenotypically different from those who are ANCA negative.

This question was addressed by Sinico et al (17), who performed a retrospective analysis of 93 patients diagnosed with CSS between 1989 and 2004. In that study, 35 patients (37.6%) were ANCA positive. Patients with CSS who were ANCA positive were significantly more likely to have disease manifestations associated with small-vessel vasculitis, including purpura (25.7% versus 6.9%; $P = 0.015$), pulmonary hemorrhage (20.0% versus 0.0%; $P = 0.001$), mononeuritis multiplex (51.4% versus 24.1%; $P = 0.013$), and renal involvement (51.4% versus 12.1%; $P < 0.001$). Patients who were ANCA negative were significantly more likely to have parenchymal lung and cardiac involvement (34.3% versus 60.3%; $P = 0.019$ and 5.7% versus 22.4%; $P = 0.042$, respectively).

These findings are supported by a recent study by Sablé-Fourtassou et al (18) that retrospectively analyzed 112 patients with CSS enrolled in clinical trials sponsored by the French Vasculitis Study Group from 1994 to 2002. In that study, 43 patients (38%) were ANCA positive. Whereas ANCA-positive patients were significantly more likely to have glomerulonephritis and neurologic disease, ANCA-negative patients were more likely to have cardiac involvement (Table 1). Furthermore, of the 71 patients with biopsy-proven CSS, vasculitis was noted more frequently among patients who were ANCA positive (69%

versus 40%; $P = 0.01$) and had more active disease. However, in terms of mortality and number of relapses, patient outcomes did not differ significantly by ANCA status.

From these 2 studies, it is tempting to postulate that CSS actually represents the confluence of 2 separate phenomena: the first an ANCA-associated process that leads to vasculitic manifestations (such as glomerulonephritis and neuropathy), and the second an eosinophil-driven process that leads to cardiopulmonary manifestations. Overlap between these phenotypes, however, is common, and the true significance of ANCA for patients with this syndrome remains unanswered.

Treatment

Should renal transplantation be postponed in patients with AAV until the ANCA is negative? In 1999, 11 retrospective case series were examined in a pooled analysis that included a total of 127 patients who underwent renal transplantation for end-stage renal failure due to AAV (mean of 11.5 patients per study) (19). The overall percentage of patients who flared during variable lengths of followup was 17.3%. The mean time from transplantation to relapse was 31 months. Sixty percent of the disease flares involved the kidney, and most AAV relapses responded well to treatment.

Unfortunately, because the identification of patients with disease relapses after transplantation was incomplete, analysis of the relapse rate among patients who were ANCA positive at the time of transplantation could be conducted in only 39 (31%) patients. Among the patients known to have circulating ANCA at the time of transplantation, recurrent disease occurred in 10 patients (25.6%). This figure is not different from the outcome among patients who were ANCA negative when they underwent renal transplantation ($P = 0.75$ for comparison; raw data not shown).

In the Collaborative Transplant Study (a registry coordinated by the University of Heidelberg that includes 400

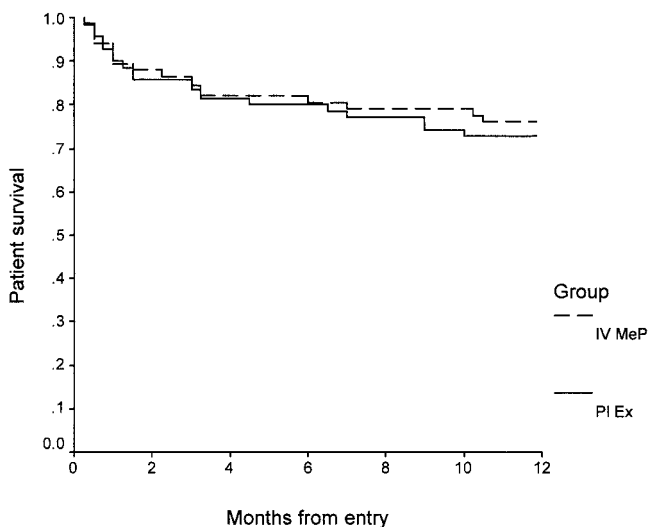


Figure 3. Patient survival in a randomized trial of plasma exchange (PI Ex) versus methylprednisolone (MeP) for severe renal vasculitis. Approximately 25% of patients in both treatment groups died within 1 year of entering the trial. IV = intravenous.

transplantation centers in 45 countries), 378 patients with WG received first cadaveric renal transplants between 1985 and 2000 (20). Data on patients followed for a minimum of 10 years indicate 80.0% survival among the patient cohort (mean age at transplantation 47.2 years) and 65.2% allograft survival. These figures compare favorably with those associated with other diseases that lead to end-stage renal failure (21). With regard to risk factors for disease recurrence, it is likely that immunosuppression used to prevent allograft rejection forestalls AAV flare, but benefits of calcineurin inhibitors (cyclosporine, tacrolimus) in addition to those of older regimens have been difficult to demonstrate (20). Finally, the available data do not suggest any required minimal length of disease quiescence before renal transplantation in patients with AAV. A judicious period of disease control prior to transplantation seems prudent, but it is difficult to provide firm guidelines about the specific length of time.

Is there a role for plasma exchange in the treatment of AAV? The European Union Vasculitis Study Group (EUVAS) attempted to answer this question with a trial designed to investigate whether plasma exchange is more effective than pulse methylprednisolone in leading to dialysis independence. All patients enrolled in the trial had severe renal dysfunction (serum creatinine levels >500 μ moles/liter, corresponding to 5.8 mg/dl) (22). Patients randomized to receive plasma exchange underwent 7 exchanges over 2 weeks. Those who were randomized to pulse methylprednisolone received 1 gm/day intravenously for 3 days. Patients in both groups received background treatment consisting of daily cyclophosphamide (CYC; 2.5 mg/kg/day) and prednisolone (60 mg/day).

The investigators randomized 137 patients to receive either plasma exchange or intravenous methylprednisolone (Figure 3). The results with regard to both mortality and renal survival were sobering. A total of 35 patients (26%) died during the trial, 23 (17%) during the first

3 months. Among all patients enrolled, only 52% (71 of 137) had independent renal function 12 months after randomization (45% in the methylprednisolone group, 59% in the plasma exchange group; $P = 0.125$). Recovery of renal function was faster among the patients who received plasma exchange ($P = 0.001$), but the serum creatinine levels at the end of the trial were not different between the 2 groups.

Pharmacotherapy

Are short courses of cyclophosphamide effective for the treatment of AAV? In recent years, a new strategy for the treatment of AAV has emerged. Patients with AAV are now frequently treated in 2 phases. During the first phase, remission is induced by using a limited course of daily oral CYC. During the second phase, remission is maintained by a prolonged course of a less toxic agent, such as methotrexate (MTX) or AZA (23).

This strategy was examined in CYCAZAREM (Cyclophosphamide or Azathioprine as a Remission therapy for vasculitis), a prospective, randomized, multicenter study conducted by the European Vasculitis Study Group (24). This open-label trial enrolled patients with new diagnoses of WG or MPA. The remission-induction regimen was a combination of daily CYC (2 mg/kg/day) and prednisolone (starting at 1 mg/kg/day) for at least 3 months. Patients who achieved disease remission were randomized to either continuing CYC at a lower dose (1.5 mg/kg/day) or beginning AZA at 2 mg/kg/day for a total of 12 months. After randomization, prednisolone was continued at a fixed dosage of 10 mg/day for the entire 12-month period. Twelve months after randomization, all patients were switched to AZA 1.5 mg/kg/day and a fixed dosage of 7.5 mg of prednisolone per day. The overall length of followup was 18 months.

Remission induction was achieved in 144 (93%) of the 155 patients. These 144 patients were randomized. The relapse rate at 18 months was not significantly different in the 2 treatment arms: 16% of the patients in the AZA group relapsed, compared with 14% of those in the CYC group ($P = 0.65$). Ten percent of patients experienced severe or life-threatening events during the remission induction phase. During the remission maintenance phase, the occurrence of severe or life-threatening adverse events did not differ between the CYC- and AZA-treated groups (10% versus 11%; $P = 0.94$).

Are TNF inhibitors effective in the treatment of ANCA-associated vasculitis? The Wegener's Granulomatosis Etanercept Trial (WGET) (25) provides strong evidence that etanercept is not effective in this disease. This trial was designed to examine the ability of etanercept to maintain disease remission during and after the tapering of conventional immunosuppressive agents (26). In addition to etanercept or placebo, all patients received standard WG therapies. Following remission, standard medications were tapered according to protocol. Eight centers in the US enrolled 180 patients with WG, and the mean followup for the overall WGET cohort was 27 months.

Of the 174 patients who could be evaluated for the

primary outcome, 126 (72.4%) achieved sustained remissions, but only 86 (49.4%) maintained this state for the remainder of the trial. There were no differences between the etanercept and control groups in the percentage of patients who achieved sustained remissions (69.7% versus 75.3%; $P = 0.39$), the percentage who achieved sustained periods of low disease activity (86.5% versus 90.6%), or time required to achieve those measures. Disease flares were common in both groups, with a total of 118 flares in the etanercept group (23 severe, 95 limited) and 134 in the control group (25 severe, 109 limited). The relative risk of disease flare per 100 person-years was 0.89 ($P = 0.54$).

With regard to adverse events, 50% of the patients overall experienced at least 1 severe or life-threatening adverse event (including 6 deaths). There were no differences between the etanercept and comparison groups for most major adverse event categories. It is notable, however, that 6 etanercept-treated patients (versus 0 controls) developed solid malignancies ($P = 0.01$) (27). All 6 of the etanercept-treated patients who developed solid malignancies were also treated with CYC during WGET. It is possible that the combination of TNF inhibition and CYC use heightens the risk of cancer beyond that observed with CYC use alone.

Given the efficacy of etanercept in several other rheumatologic diseases, and the rationale for the use of TNF inhibition in WG, the negative results of WGET are noteworthy. There may be differences in efficacy among the various approaches to the inhibition of TNF (28). The limited data available on the use of infliximab in WG, however, raise concerning issues, particularly with regard to the frequency of disseminated infection and relapse associated with infliximab therapy (29–31).

Do early-generalized AAV patients treated with MTX fare as well as those treated with CYC? The realization more than a decade ago (32) that remission may be induced in some patients with WG without CYC was an important advance in the treatment of vasculitis (33–35). Some studies, however, noted a high frequency of flares following initial periods of disease control. Longer followup of MTX-treated patients raised the following question: Would these patients have fared better if treated initially with CYC?

This question was examined by de Groot et al (36), who conducted an unblinded, prospective controlled trial of 100 patients with early-generalized AAV (roughly comparable with the limited groups of patients studied in a National Institutes of Health [NIH] series [37] and in the WGET [25]). Patients in the Non-Renal Alternative with Methotrexate (NORAM) trial were randomized to receive remission induction therapy with glucocorticoids combined with either MTX or CYC. In both groups, patients' prednisolone dosage was tapered to 7.5 mg/day by 6 months and discontinued entirely by 12 months of treatment.

At 6 months, the remission rates in both groups were not statistically different. The remission rate was 89.8% in the MTX group and 93.5% in the CYC group ($P = 0.78$). Relapse within 18 months or earlier, however, was more frequent among patients whose remissions were induced with MTX (69.5%) than among the CYC-treated patients

(46.5%; $P = 0.02$). Moreover, the median cumulative prednisolone dosage in the MTX group was 8.8 gm, considerably higher than the median cumulative dosage of 6.2 gm in the CYC group ($P = 0.001$). It is worth noting that most disease flares in this trial occurred after discontinuation of immunosuppression (including glucocorticoids).

Remission Maintenance

When should remission maintenance agents be stopped for patients with AAV? A sizeable minority of patients achieve prolonged periods of disease-free remissions following courses of conventional induction therapy. In the NIH longitudinal cohort (37), approximately one-third of the patients were “cured” after their first course of treatment with daily CYC and glucocorticoids. Unfortunately, at present we have no means of distinguishing patients who will require ongoing therapy from those who may do well off treatment. Some evidence indicates that patients who remain ANCA negative after therapy are less likely to flare, although this is not always the case (38).

One point that has emerged from CYCAZAREM (24) is that among AAV diseases, WG is more likely than MPA to flare. In that trial, relapse was less common among patients with MPA (4 [8%] of 52 patients) than among those with WG (17 [18%] of 92; $P = 0.03$). No other baseline variables in that study increased the risk of relapse.

Clinical trials in AAV completed over the past 2 years have also demonstrated the value of low-dose glucocorticoids for remission maintenance in patients with AAV (24,25,36). In CYCAZAREM, following initially high doses of prednisolone, patients did not taper off glucocorticoids entirely. Not surprisingly, the CYCAZAREM investigators reported a flare rate much lower than those detected in the WGET (25) and NORAM (36). The prolonged use of low-dose glucocorticoids in CYCAZAREM is probably the main reason that fewer disease flares were observed in that trial.

Prognosis and Outcomes

What are the long-term risks of Buerger's disease (thromboangiitis obliterans)? Buerger's disease typically affects the extremities, sparing internal organs but leading to claudication, ischemic ulcers, and digital infarction. Although the cause of Buerger's disease is unknown, it is strongly associated with tobacco use. Complete cessation of tobacco use is considered an effective treatment strategy, but the long-term risks of Buerger's disease have not been studied in detail.

The long-term complications of Buerger's disease were addressed by Cooper et al (39), who reviewed the records of 344 patients diagnosed with Buerger's disease evaluated at the Mayo Clinic between 1976 and 1999. A total of 233 of the patients (67.7%) initially considered for this study were excluded because of the presence of other potential causes of arterial disease (e.g., trauma, atherosclerosis, diabetes). Of the 111 patients with no other cause of arterial damage, 88 were still alive at the time of the study. The survivors were surveyed by mail regarding amputations and nicotine use.

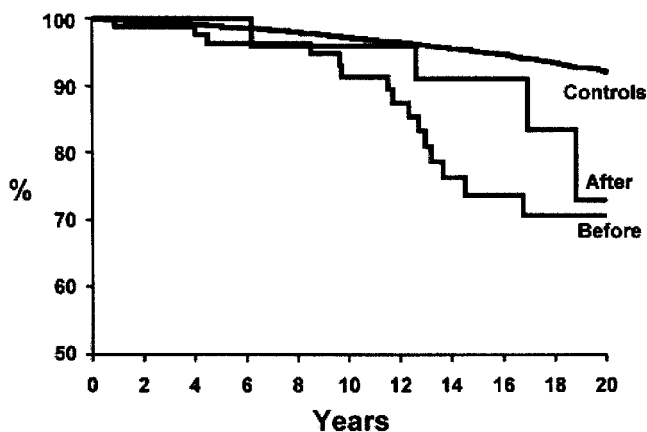


Figure 4. Mortality associated with Buerger's disease before and after smoking cessation. Reproduced, with permission, from ref. 39.

From time of diagnosis, the risk of amputation was 25% at 5 years and 38% at 10 years. Cessation of tobacco exposure significantly decreased the risk of amputation. The amputation rate, 84.3 amputations per 1,000 person-years for patients who were active smokers, dropped to 30.6 amputations per 1,000 person-years for those who quit smoking. The increased risk of amputation associated with Buerger's disease was eliminated entirely 8 years after smoking cessation.

Survival among the patients with Buerger's disease in this study was significantly lower than the expected survival based on age- and sex-specific survival rates in the US ($P < 0.001$). In contrast to amputation risk, long-term survival was not significantly improved among patients who stopped using tobacco products (Figure 4). The mean \pm SD age at death among the patients with Buerger's disease (regardless of smoking status) was 52.2 ± 8.9 years.

Are patients with systemic vasculitis at increased risk of venous thromboembolism? The systemic vasculitides are generally described in terms of their pattern of arterial involvement. It may be important, however, to consider the presence of venous involvement as well, especially because the vessel damage incurred by patients with systemic vasculitis might result in increased thromboembolic risk.

Venous obstruction, in the form of superior and inferior vena cava occlusion, Budd-Chiari syndrome, and venous thrombosis, is a known complication of Behçet's disease (40,41). Venous thromboembolic disease has also been reported as a manifestation of Buerger's disease (42); superficial thrombophlebitis is often the herald lesion in this disorder (43). One recent study of 36 patients with Buerger's disease noted that 8 patients (22%) carried the factor V Leiden mutation (44). Another study of 47 patients with Buerger's disease noted that 17 (36%) had detectable levels of anticardiolipin antibodies, and that patients with anticardiolipin antibodies were at higher risk of amputation than those without anticardiolipin antibodies (100% versus 17%; $P = 0.003$) (45).

Finally, a recent analysis indicated that venous thrombotic events (VTE) may also be a problem among patients

with WG (46). An analysis of 180 patients in the WGET led to the observation that 13 (7.2%) had had histories of VTE prior to enrollment. During the trial, an additional 16 patients developed new episodes of VTE. The incidence of VTE among patients with WG who had not experienced VTE before enrollment was 7.0 per 100 person-years (95% CI 0.63–77.9), 7 times greater than the incidence noted among patients with systemic lupus erythematosus (46) (Figure 5). The median time from enrollment to VTE was 2 months, implying that venous thromboembolism may be a previously unsuspected manifestation of disease flare among patients with WG.

Summary

The incidence of AAV appears to be stable rather than increasing, but the incidence of AAV may vary considerably according to geography. In contrast, there are conflicting data about the incidence of rheumatoid vasculitis and whether it is increasing or decreasing. The impact of biologic agents on the incidence of rheumatoid vasculitis is not yet clear.

Leukotriene inhibitors do not cause CSS, but may permit "successful" glucocorticoid tapers that unmask the underlying disorder. ANCA status may be helpful in predicting the clinical phenotype in CSS, but overlapping clinical features indicate that factors other than ANCA are essential to the definition of phenotype in that disease.

Renal transplant is appropriate for patients with inactive WG, regardless of ANCA status. Plasma exchange is a reasonable intervention for patients with AAV who present with end-stage or near end-stage renal disease. The

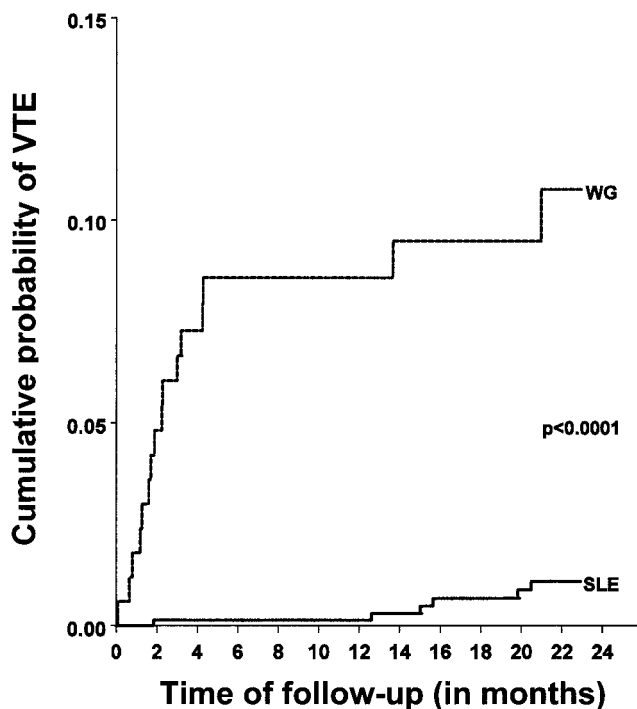


Figure 5. Time to first venous thrombotic event (VTE) among patients with Wegener's granulomatosis (WG) versus patients with systemic lupus erythematosus (SLE). Reproduced, with permission, from ref. 46.

impact of this treatment on long-term renal outcomes is probably modest, however, and patients who present with advanced renal dysfunction are at high risk of mortality.

Three- to six-month courses of CYC for remission induction (followed by treatment with remission maintenance agents) are as effective as longer courses of CYC for the treatment of AAV. MTX (plus glucocorticoids) is equally effective as CYC (plus glucocorticoids) in the induction of remission for patients with early generalized AAV, but MTX is associated with a higher risk of disease flare. Etanercept is not an effective therapy for WG.

Because not all patients with AAV will experience disease flares following the achievement of remission, the continuation of remission maintenance agents indefinitely for all patients is not advised. For patients who demonstrate a tendency to flare, however, longstanding regimens for the maintenance of remission may be required. Low-dose glucocorticoids may be a valuable adjunct to remission-maintenance regimens.

VTE is an underappreciated complication of WG, and may be a direct consequence of the disease.

Patients with Buerger's disease have increased mortality, whether or not they stop smoking.

AUTHOR CONTRIBUTIONS

Dr. Stone had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Seo, Stone.

Acquisition of data. Seo, Stone.

Analysis and interpretation of data. Seo, Stone.

Manuscript preparation. Seo, Stone.

REFERENCES

- Seo P, Stone JH. Large-vessel vasculitis. *Arthritis Rheum* 2004;51:128–39.
- Gonzalez-Gay MA, Garcia-Porrua C, Guerrero J, Rodriguez-Ledo P, Llorca J. The epidemiology of the primary systemic vasculitides in northwest Spain: implications of the Chapel Hill Consensus Conference definitions. *Arthritis Rheum* 2003;49:388–93.
- Koldingsnes W, Nossent H. Epidemiology of Wegener's granulomatosis in northern Norway. *Arthritis Rheum* 2000;43:2481–7.
- Carruthers DM, Watts RA, Symmons DP, Scott DG. Wegener's granulomatosis: increased incidence or increased recognition? *Br J Rheumatol* 1996;35:142–5.
- Watts RA, Lane SE, Mooney J, Scott DG. Epidemiology of primary systemic vasculitis: unchanged over 15 years [abstract]. *Arthritis Rheum* 2004;50 Suppl 9:S270.
- Watts RA, Lane SE, Bentham G, Scott DG. Epidemiology of systemic vasculitis: a ten-year study in the United Kingdom. *Arthritis Rheum* 2000;43:414–9.
- Reinhold-Keller E, Herlyn K, Wagner-Bastmeyer R, Gross WL. Stable incidence of primary systemic vasculitides over five years: results from the German vasculitis register. *Arthritis Rheum* 2005;53:93–9.
- O'Dell JR. Therapeutic strategies for rheumatoid arthritis. *N Engl J Med* 2004;350:2591–602.
- Turesson C, Jacobsson LT. Epidemiology of extra-articular manifestations in rheumatoid arthritis. *Scand J Rheumatol* 2004;33:65–72.
- Turesson C, McClelland RL, Christianson TJ, Matteson EL. No decrease over time in the incidence of vasculitis or other extraarticular manifestations in rheumatoid arthritis: results from a community-based study. *Arthritis Rheum* 2004;50:3729–31.
- Watts RA, Lane SE, Scott DG. Decrease over time in the incidence of systemic rheumatoid vasculitis [letter]. *Arthritis Rheum* 2005;52:1620–1.
- Wechsler ME, Garpestad E, Flier SR, Kocher O, Weiland DA, Polito AJ, et al. Pulmonary infiltrates, eosinophilia, and cardiomyopathy following corticosteroid withdrawal in patients with asthma receiving zafirlukast. *JAMA* 1998;279:455–7.
- DuMouchel W, Smith ET, Beasley R, Nelson H, Yang X, Fram D, et al. Association of asthma therapy and Churg-Strauss syndrome: an analysis of postmarketing surveillance data. *Clin Ther* 2004;26:1092–104.
- Keogh KA, Specks U. Churg-Strauss syndrome: clinical presentation, antineutrophil cytoplasmic antibodies, and leukotriene receptor antagonists. *Am J Med* 2003;115:284–90.
- Katsura T, Yoshida F, Takinishi Y. The Churg-Strauss syndrome after pranlukast treatment in a patient not receiving corticosteroids. *Ann Intern Med* 2003;139:386–7.
- Guillevin L, Cohen P, Gayraud M, Lhote F, Jarrousse B, Casassus P. Churg-Strauss syndrome: clinical study and long-term follow-up of 96 patients. *Medicine (Baltimore)* 1999;78:26–37.
- Sinico RA, Di Toma L, Maggiore U, Bottero P, Radice A, Tosini C, et al. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. *Arthritis Rheum* 2005;52:2926–35.
- Sable-Fourtassou R, Cohen P, Mahr A, Pagnoux C, Mouthon L, Jayne D, et al. Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. *Ann Intern Med* 2005;143:632–8.
- Nachman PH, Segelmark M, Westman K, Hogan SL, Satterly KK, Jennette JC, et al. Recurrent ANCA-associated small vessel vasculitis after transplantation: a pooled analysis. *Kidney Int* 1999;56:1544–50.
- Schmitt WH, Opelz G, van der Woude FJ. Renal transplantation (RTx) is safe and successful in Wegener's granulomatosis (WG): data from the Collaborative Transplant Study [abstract]. *J Am Soc Nephrol* 2002;13:564A–5.
- Schmitt WH, van der Woude FJ. Organ transplantation in the vasculitides. *Curr Opin Rheumatol* 2003;15:22–8.
- Jayne DR, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol* 2007;18:2180–8.
- Seo P, Stone JH. The antineutrophil cytoplasmic antibody-associated vasculitides. *Am J Med* 2004;117:39–50.
- Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JW, Dadonienė J, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med* 2003;349:36–44.
- Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. *N Engl J Med* 2005;352:351–61.
- WGET Research Group. Design of the Wegener's Granulomatosis Etanercept Trial (WGET). *Control Clin Trials* 2002;23:450–68.
- Stone JH, Holbrook JT, Marriott MA, Tibbs AK, Sejismundo LP, Min YI, et al, for the Wegener's Granulomatosis Etanercept Trial Research Group. Solid malignancies among patients in the Wegener's Granulomatosis Etanercept Trial. *Arthritis Rheum* 2006;54:1608–18.
- Van den Brande JM, Braat H, van den Brink GR, Versteeg HH, Bauer CA, Hoedemaeker I, et al. Infliximab but not etanercept induces apoptosis in lamina propria T-lymphocytes from patients with Crohn's disease. *Gastroenterology* 2003;124:1774–85.
- Booth A, Harper L, Hammad T, Bacon P, Griffith M, Levy J, et al. Prospective study of TNFalpha blockade with infliximab in anti-neutrophil cytoplasmic antibody-associated systemic vasculitis. *J Am Soc Nephrol* 2004;15:717–21.
- Bartolucci P, Ramanoelina J, Cohen P, Mahr A, Godmer P, Le Hello C, et al. Efficacy of the anti-TNF-alpha antibody infliximab against refractory systemic vasculitides: an open pilot

- study on 10 patients. *Rheumatology (Oxford)* 2002;41:1126–32.
31. Lamprecht P, Voswinkel J, Lilienthal T, Nolle B, Heller M, Gross WL, et al. Effectiveness of TNF-alpha blockade with infliximab in refractory Wegener's granulomatosis. *Rheumatology (Oxford)* 2002;41:1303–7.
 32. Hoffman GS, Leavitt RY, Kerr GS, Fauci AS. The treatment of Wegener's granulomatosis with glucocorticoids and methotrexate. *Arthritis Rheum* 1992;35:1322–9.
 33. Langford CA, Talar-Williams C, Sneller MC. Use of methotrexate and glucocorticoids in the treatment of Wegener's granulomatosis: long-term renal outcome in patients with glomerulonephritis. *Arthritis Rheum* 2000;43:1836–40.
 34. De Groot K, Muhler M, Reinhold-Keller E, Paulsen J, Gross WL. Induction of remission in Wegener's granulomatosis with low dose methotrexate. *J Rheumatol* 1998;25:492–5.
 35. Sneller MC, Hoffman GS, Talar-Williams C, Kerr GS, Hallahan CW, Fauci AS. An analysis of forty-two Wegener's granulomatosis patients treated with methotrexate and prednisone. *Arthritis Rheum* 1995;38:608–13.
 36. De Groot K, Rasmussen N, Bacon PA, Tervaert JW, Feighery C, Gregorini G, et al, for the European Vasculitis Study Group. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2005;52:2461–9.
 37. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, et al. Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med* 1992;116:488–98.
 38. Slot MC, Tervaert JW. Wegener's granulomatosis. *Autoimmunity* 2004;37:313–5.
 39. Cooper LT, Tse TS, Mikhail MA, McBane RD, Stanson AW, Ballman KV. Long-term survival and amputation risk in thromboangiitis obliterans (Buerger's disease). *J Am Coll Cardiol* 2004;44:2410–1.
 40. Ames PR, Steuer A, Pap A, Denman AM. Thrombosis in Behçet's disease: a retrospective survey from a single UK centre. *Rheumatology (Oxford)* 2001;40:652–5.
 41. Bayraktar Y, Balkanci F, Bayraktar M, Calguneri M. Budd-Chiari syndrome: a common complication of Behçet's disease. *Am J Gastroenterol* 1997;92:858–62.
 42. Fischer MD, Hopewell PC. Recurrent pulmonary emboli and Buerger's disease. *West J Med* 1981;135:238–41.
 43. Stone JH, Calabrese LH, Hoffman GS, Pusey CD, Hunder GG, Hellmann DB. Vasculitis: a collection of pearls and myths. *Rheum Dis Clin North Am* 2001;27:677–728, v.
 44. Avcu F, Akar E, Demirkilic U, Yilmaz E, Akar N, Yalcin A. The role of prothrombotic mutations in patients with Buerger's disease. *Thromb Res* 2000;100:143–7.
 45. Maslowski L, McBane R, Alexewicz P, Wysokinski WE. Antiphospholipid antibodies in thromboangiitis obliterans. *Vasc Med* 2002;7:259–64.
 46. Merkel PA, Lo GH, Holbrook JT, Tibbs AK, Allen NB, Davis JC, et al. Brief communication: high incidence of venous thrombotic events among patients with Wegener granulomatosis: the Wegener's Clinical Occurrence of Thrombosis (WeCLOT) Study. *Ann Intern Med* 2005;142:620–6.