Published in final edited form as:

Curr Rheumatol Rep. 2010 December ; 12(6): 414–419. doi:10.1007/s11926-010-0130-1.

Rheumatoid Vasculitis: Vanishing Menace or Target for New Treatments?

C. M. Bartels and

University of Wisconsin-Madison School of Medicine and Public Health; William S. Middleton Memorial Veterans Hospital-Madison, Madison, WI, USA, cb4@medicine.wisc.edu

A. J. Bridges

University of Wisconsin-Madison School of Medicine and Public Health; William S. Middleton Memorial Veterans Hospital-Madison, 2500 Overlook Terrace, Madison, WI 53705, USA, alan.bridges@va.gov

Abstract

Rheumatoid vasculitis is a rare but serious complication of rheumatoid arthritis. Herein we examine the pathophysiology, epidemiology, clinical diagnosis, and treatment of rheumatoid vasculitis. Seropositivity, specific HLA variations, and tobacco use are among the genetic and environmental predictors of rheumatoid vasculitis. Fortunately, recent reports have noted declines in the prevalence of rheumatoid vasculitis. Nevertheless, proper recognition of systemic manifestations may assist in pathologically confirming the diagnosis, determining the extent of disease, and guiding treatment. Contemporary treatment reports are discussed in the context of the ongoing debate regarding whether new agents may trigger, treat, or even prevent rheumatoid vasculitis. Evolving genetic, histopathologic, and immunologic studies partnered with ongoing clinical experience with biologics offer promise to inform future prevention and treatment of rheumatoid vasculitis.

Keywords

Rheumatoid arthritis; Rheumatoid vasculitis; Epidemiology; Biologic therapy

Introduction

Rheumatoid vasculitis is arguably the most serious systemic disease manifestation of rheumatoid arthritis (RA). Rheumatoid vasculitis manifests almost exclusively in patients with rheumatoid autoantibodies and often occurs in the context of other extra-articular manifestations. A diagnosis is most easily attainable when it involves the skin or peripheral nerves. Internal organ involvement is very serious but often more difficult to diagnose. In addition, rheumatoid vasculitis may be mimicked by atherosclerotic vascular disease, an increasingly recognized complication of systemic RA. Biopsy is typically required to ensure a definitive diagnosis of rheumatoid vasculitis, particularly given the high risk of treatment-related toxicity. Although a validated definition does not exist, for the purposes of this article, and consistent with features originally described by Scott et al. [1], we define rheumatoid vasculitis as a clinicopathologic manifestation of RA characterized by tissue damage or ischemia verified pathologically by vasculitis.

Disclosure Dr. Bridges has served on advisory boards for UCB and Genentech and has received honoraria from, received payment for development of educational presentations (including service on speakers' bureaus) from, and had travel/accommodation expenses covered by Abbott Laboratories, Genentech, and Bristol-Myers Squibb. No other potential conflicts of interest relevant to this article were reported.

Once a more common cause for hospitalization among RA patients, the prevalence of rheumatoid vasculitis is now decreasing [2••]. Improved control of RA in the era of biologic therapy may be a potential explanation. Most recent articles regarding rheumatoid vasculitis describe case series or case reports of rare manifestations or outcomes related to novel biologic therapy. In this review, we provide an overview of recent pathogenic associations, the range of clinical organ system involvement, and contemporary therapeutic considerations for rheumatoid vasculitis.

Pathophysiology and Epidemiology

Pathology and Pathogenesis

Rheumatoid vasculitis occurs almost exclusively in patients with seropositive nodular RA [3-5]. Studies have used this clinical clustering to better understand the genetics of RA. RA studies have focused on *HLA-DRB1*, specifically the alleles with a conserved amino acid sequence in the third hypervariable region, termed the *shared epitope*. A recent meta-analysis that compiled 14 studies encompassing more than 1500 RA patients revealed a striking relationship between rheumatoid vasculitis and three specific genotypes of the *HLA-DRB1* shared epitope: *0401/*0401, *0401/*0404, and *0101/*0401 [5].

With the shared epitope as the genetic background, a search for potential triggers of rheumatoid vasculitis has largely focused on an association with smoking. A recent large study of the Mayo Clinic Rochester Epidemiology Project and several Swedish cohorts suggest a strong association of smoking with the development of rheumatoid vasculitis [6]. Other studies have supported this association not only in rheumatoid vasculitis but also in other extra-articular manifestations. The Mayo study also described a new association of *HLA-C3* with rheumatoid vasculitis that was not due to linkage disequilibrium with *HLA-DRB1* [6]. That study highlighted the heterogeneity of genetic, environmental, and clinical features of RA extra-articular disease. It is clear that we have not solved the puzzle of the pathogenesis of RA and rheumatoid vasculitis.

The association of rheumatoid vasculitis with rheumatoid factor and antitissue antibodies (eg, anti-cyclic citrullinated polypeptide [CCP], antinuclear antibodies) suggests that immune complex disease may be causative [7]. Immune complexes may be found in affected tissue, and most patients with rheumatoid vasculitis have circulating autoantibodies. However, many patients with RA who have circulating or tissue-deposited immune complexes and high levels of autoantibodies do not develop vasculitis. The relationship of these immune complexes to RA and vasculitis leaves many unanswered questions and is far from definitive.

Decisively, RA is a systemic inflammatory disease with pathology reflecting the widespread impact of inflammation. Uncontrolled systemic inflammation promotes early and more aggressive atherosclerotic vascular disease that may mimic vasculitis manifestations. This strongly supports the requirement for histopathologic confirmation of vasculitis. Pathologic features of rheumatoid vasculitis include mononuclear cells or neutrophilic infiltration of the vessel wall of small and medium vessels. Features of vessel wall destruction are often found, including necrosis, leukocytoclasia, and disruption of the internal and external elastic lamina. An important observation is that inflammation of greater than three cell layers of the vessel is a sensitive and specific finding to distinguish rheumatoid vasculitis from RA without vasculitis [8]. Perivascular infiltrates that do not involve the vessel wall may be seen in RA without vasculitis and should not be used as a histologic finding to support a diagnosis of vasculitis. In addition, capillaritis manifest as nailfold infarcts or by histopathology is common in RA and should not be construed as a feature of rheumatoid vasculitis.

Prevalence and Epidemiology

The prevalence of rheumatoid vasculitis has been reported to be declining, although individual patient characteristics may affect risk [2•,3,9]. Case-control studies have suggested that in addition to rheumatoid factor and CCP positivity, male gender, tobacco use, rheumatoid nodules, and older onset or long disease duration confer added risk [3,9]. Clinical reports have estimated the prevalence of RA vasculitis at less than 1% to 5% [10-12], whereas autopsy studies have reported 15% to 31% [13]. Contemporary trends in rheumatoid vasculitis have been debated. A US hospital-based study [14] and a United Kingdom population-based cohort study [15,16] reported declines in RA vasculitis cases, whereas one US community-based study reported no such declines [17]. A recent US nationwide, retrospective cohort study concluded that the prevalence of RA vasculitis has been declining over the past decades [2•]. In that study, steep declines in observed prevalence rates of RA vasculitis were noted in the inpatient and outpatient settings around the year 2000, raising questions of whether this may be causally linked to improved treatments of RA.

The morbidity and mortality of rheumatoid vasculitis are substantial. Studies have shown that the 5-year mortality rate is 30% to 50%, with even higher rates of morbidity related to disease complications or vasculitis treatment-related toxicity [18,19]. This makes it imperative to properly diagnose rheumatoid vasculitis and select the most appropriate treatment to limit adverse events.

Clinical Manifestations and Diagnosis

Organ System Manifestations

Rheumatoid vasculitis may involve virtually any organ of the body (Table 1). The most common sites of involvement are the skin and peripheral nerves. In many series, the skin or peripheral nerves are involved in more than 80% of patients [20]. Major organ system involvement of the heart, bowel, or kidney is much less common but can lead to significant morbidity and mortality, including myocardial infarction, bowel ischemia, and renal failure. Although central nervous system involvement is rare, many case reports describe its occurrence [21,22].

Cutaneous manifestations of rheumatoid vasculitis include palpable purpura, nodules, ulcers (Fig. 1), and digital necrosis [23]. Livedo reticularis is commonly seen, although it is nonspecific and is found in multiple other disorders. When skin findings are present, a careful search for other systemic manifestations is necessary to characterize the severity of the vasculitis presentation. Skin involvement without other organ system involvement carries a more favorable prognosis.

The next most common organ involved is the peripheral nervous system. Distal symmetric sensory polyneuropathy, distal motor or combined neuropathy, or mononeuritis multiplex encompass the range of peripheral nervous system manifestations. Mononeuritis multiplex is very specific to systemic vasculitis, and biopsy of an affected nerve will have a high yield.

Clinical Approach to Suspected Rheumatoid Vasculitis

Discovering skin or nervous system abnormalities in a patient with extra-articular manifestations of RA and constitutional symptoms (eg, weight loss or fever) should raise a high index of suspicion for rheumatoid vasculitis and must prompt further evaluation. Options for definitive diagnosis include biopsy of involved skin, a muscle and nerve biopsy of an affected territory, or biopsy of another affected organ. Biopsy of skin lesions has the highest yield (up to 75%). Electrophysiologic study of peripheral nerves may reveal subclinical defects that could be used to direct a biopsy. We have found that sural or peroneal nerve and

gastrocnemius or peroneus brevis muscle biopsies can be completed with minimal morbidity and good yield. Other studies recommend rectus femoris muscle biopsy [24]. Blind rectal biopsy is not commonly pursued today. Even in patients with neuropathy, the diagnostic yield of muscle or nerve biopsy may be less than 50% [8]. Although angiogram may reveal classic findings of polyarteritis nodosa when medium vessel involvement occurs in rheumatoid vasculitis, angiographic findings are nonspecific and should not be substituted for a tissue-confirmed diagnosis, except in the setting of bowel ischemia.

A complete review of systems and organ system staging should be performed at initial diagnosis to assess the extent of disease (extra-articular manifestations and/or vasculitis organ system involvement). This survey will direct therapy given that greater degree of systemic or serious organ system involvement necessitates more aggressive therapy.

Laboratory tests may support, but do not confirm, a diagnosis of systemic RA or rheumatoid vasculitis. Laboratory findings may include anemia of chronic inflammation, elevation of erythrocyte sedimentation rate or C-reactive protein, polyclonal hypergammaglobulinemia, and RA-associated autoantibodies. Complement levels may be dynamically decreased during active disease and, along with inflammatory parameters, may provide useful follow-up information. Moreover, the presence of ongoing tissue ischemia without evidence of systemic inflammation should lead to consideration of ischemia related to arteriosclerotic or diabetic microvascular disease. As shown in Figure 1, a location on the dorsal feet or shins in distinction from more distal locations may help distinguish rheumatoid vasculitis ulcers from other sources of vascular insufficiency.

Some studies have shown an association between elevated rheumatoid factor or anti-CCP antibodies and rheumatoid vasculitis. However, the high prevalence of these antibodies in RA without vasculitis lends little to a positive predictive value for the diagnosis of rheumatoid vasculitis [7]. Conversely, a lack of rheumatoid autoantibodies may confer a negative predictive value for rheumatoid vasculitis, as one study showed that more than 90% of patients with rheumatoid vasculitis had anti-CCP antibodies, compared with 7% of patients with other types of systemic vasculitis [7]. The prevalence of anti-CCP antibodies is low in the general population and patients with atherosclerotic vascular disease, adding further to the negative predictive value of anti-CCP antibody negativity.

Antineutrophil cytoplasmic antibodies (ANCA) are found in 50% to 85% of patients with primary small vessel vasculitides such as Wegener's granulomatosis, microscopic polyarteritis, and Churg-Strauss vasculitis. Unfortunately, ANCA is not specific for these types of systemic vasculitis. In one study, an atypical perinuclear ANCA was found in 48% of patients with rheumatoid vasculitis [25]. Specific enzyme immunoassay studies for antimyeloperoxidase and anti-proteinase-3 should be performed and are typically negative in rheumatoid vasculitis.

In summary, characteristic histopathology confirmation of vasculitis is generally necessary for a diagnosis of rheumatoid vasculitis. Other clinical and laboratory features are often supportive and may be used to assist follow-up.

Treatment

The aggressiveness of treatment for rheumatoid vasculitis is typically determined by the degree of organ system involvement. Mild rheumatoid vasculitis involving the skin or peripheral nerves can be treated with prednisone and methotrexate or azathioprine. More serious organ system involvement may require treatment with higher-dose steroids and cyclophosphamide or biologic agents (Table 2).

Prednisone therapy is essential to initially decrease systemic inflammation. The dose depends on the degree of systemic inflammation and the level of organ system involvement. Typical doses range from 30 to 100 mg twice daily at onset. We typically use twice-daily dosing for 2 to 4 weeks, with maximal doses of 250 mg intravenously twice daily. Central nervous system involvement, acute renal failure, acute myocardial infarction, or ischemic bowel are serious manifestations that call for intravenous steroid therapy and consideration of cytotoxic or biologic agents. Cyclophosphamide and prednisone historically have been used in these severe systemic RA vasculitis cases but may confer considerable toxicity [26].

In milder cases, methotrexate is our first-line disease-modifying antirheumatic drug (DMARD) of choice to pair with prednisone. It is well-studied in RA, decreases erosive arthritis and systemic inflammation, and reports support its use in RA vasculitis [27,28]. We start with a dose of 10 mg/wk and titrate up to a dose of 20 to 25 mg/wk based on efficacy and adverse events. Although there are a few reports of exacerbation of cutaneous vasculitis or severe nodules with methotrexate therapy [29,30], this is uncommon and often can be overcome with an alternative DMARD. Azathioprine is another tested alternative in doses of 50 mg/d to 150 mg (~ 2 mg/kg per day) divided daily [31]. Care should be taken to titrate the dose while following blood counts and liver tests. The patient whose lesions are shown in Figure 1 was treated with moderate-dose steroids and azathioprine, with complete ulcer healing in 4 months.

Pragmatically, we have used biologic agents in combination with methotrexate as second-line DMARD therapy in most recent rheumatoid vasculitis cases involving systemic organs. This decision is not based on controlled trials but rather on case series supporting biologic therapy weighed against the marked toxicity of cyclophosphamide. We have successfully used tumor necrosis factor (TNF) inhibitors and rituximab as first-line treatment in severe systemic RA vasculitis.

Clinical evidence supporting the use of biologic agents consists of case reports and case series, while some other reports have raised questions of causal associations between biologic agents and RA vasculitis. An interesting case series in 2008 described nine cases of refractory rheumatoid vasculitis defined by prior cyclophosphamide failure that were treated with a TNF inhibitor [32••]. Among seven patients who completed 6 months of therapy, five achieved complete remission, and one achieved incomplete remission. Several other small case reports also describe successful treatment of rheumatoid vasculitis with anti-TNF therapy [33-38]. Conversely, a literature review published in 2007 cited 113 reported cases of vasculitis triggered by TNF-targeted treatments [39••], although several cases included isolated cutaneous leukocytoclastic vasculitis. A retrospective review at one large center with 440 patients receiving anti-TNF treatments for RA demonstrated that only 2 of 6 observed RA vasculitis cases possibly could have been causally linked to anti-TNF treatment [40••]. One must recognize that serious RA refractory to other treatments is more likely to lead to biologic treatment and more likely to lead to RA vasculitis, but the two may not be causally linked.

Case reports also describe three cases of successful use of rituximab to treat RA vasculitis [41•,42]. Again, one report suggested a possible causal link between rituximab and RA vasculitis [43]. We have used rituximab successfully in patients with high levels of autoantibodies, comorbid neutropenia, or liver disease complicating therapeutic options. The finding of high rheumatoid factor and CCP antibody titers in RA vasculitis and observed declines with successful treatment lends theoretical support to the anti-B-cell agent rituximab [44]. Its use is also supported by emerging evidence of efficacy in other types of systemic vasculitis, including Wegener's granulomatosis [45-47].

Although rheumatoid vasculitis is classically an inflammatory vascular process, we advocate aggressive treatment of traditional risk factors for atherosclerotic disease as well. Smoking

cessation should be recommended [48]. Treatment of elevated blood pressure and cholesterol is also important. A recent nationwide study reported primary lipid screening was missed in 56% of older adults with RA, suggesting that rheumatologists could be better at providing or recommending preventive care for modifiable risk factors for cardiovascular disease (Bartels et al, unpublished data).

Conclusions

Rheumatoid vasculitis is among the most serious complications of RA. Fortunately, its prevalence appears to be declining. Newer RA treatments, including biologic therapies, offer a broader array of potential therapeutic options, although no controlled trials exist to guide treatment. In general, following tissue confirmation of the diagnosis, the severity of organ involvement and disease manifestations can guide treatment decisions. Evolving genetic, histopathologic, and immunologic studies partnered with ongoing clinical experience with biologic agents offer promise to inform future prevention and treatment of rheumatoid vasculitis.

Acknowledgments

Dr. Bartels receives support from grant no. 1KL2RR025012-01, awarded through the University of Wisconsin Institute of Clinical Research KL2 Scholar Program, under 1UL1RR025011, the Clinical and Translational Science Award program of the National Center for Research Resources, National Institutes of Health.

References

1. Scott DG, Bacon PA, Tribe CR. Systemic rheumatoid vasculitis: a clinical and laboratory study of 50 cases. *Medicine* 1981;60:288–297. [PubMed: 7242322]
2. Bartels C, Bell C, Rosenthal A, et al. Decline in rheumatoid vasculitis prevalence among US veterans: a retrospective cross-sectional study. *Arthritis Rheum* 2009;60:2553–2557. [PubMed: 19714622]
This cross-sectional study examined more than 20 years of national data representing more than 37,000 RA patients annually to demonstrate the declining prevalence of rheumatoid vasculitis in the inpatient and outpatient settings, with breakpoints around 2000 suggesting a possible link to new biologic treatments.
3. Voskuyl AE, Zwinderman AH, Westedt ML, et al. Factors associated with the development of vasculitis in rheumatoid arthritis: results of a case-control study. *Ann Rheum Dis* 1996;55:190–192. [PubMed: 8712883]
4. Turesson C, O’Fallon WM, Crowson CS, et al. Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. *Ann Rheum Dis* 2003;62:722–727. [PubMed: 12860726]
5. Gorman JD, David-Vaudey E, Pai M, et al. Particular HLA-DRB1 shared epitope genotypes are strongly associated with rheumatoid vasculitis. *Arthritis Rheum* 2004;50:3476–3484. [PubMed: 15529352]
6. Turesson C, Schaid DJ, Weyand CM, et al. Association of HLA-C3 and smoking with vasculitis in patients with rheumatoid arthritis. *Arthritis Rheum* 2006;54:2776–2783. [PubMed: 16947780]
7. Laskaria K, Ahmadi-Simab K, Lamken M, et al. Are anti-cyclic citrullinated peptide autoantibodies seromarkers for rheumatoid vasculitis in a cohort of patients with systemic vasculitis? *Ann Rheum Dis* 2010;69:469–471. [PubMed: 20107034]
8. Voskuyl AE, van Duinen SG, Zwinderman AH, et al. The diagnostic value of perivascular infiltrates in muscle biopsy specimens for the assessment of rheumatoid vasculitis. *Ann Rheum Dis* 1998;57:114–117. [PubMed: 9613342]
9. Turesson C, Jacobsson LT. Epidemiology of extra-articular manifestations in rheumatoid arthritis. *Scand J Rheumatol* 2004;33:65–72. [PubMed: 15163106]

10. Kaye O, Beckers CC, Paquet P, et al. The frequency of cutaneous vasculitis is not increased in patients with rheumatoid arthritis treated with methotrexate. *J Rheumatol* 1996;23:253–257. [PubMed: 8882028]
11. Salvarani C, Macchioni P, Mantovani W, et al. Extraarticular manifestations of rheumatoid arthritis and HLA antigens in northern Italy. *J Rheumatol* 1992;19:242–246. [PubMed: 1629822]
12. Wattiaux MJ, Kahn MF, Thevenet JP, et al. Vascular involvement in rheumatoid polyarthritis. Retrospective study of 37 cases of rheumatoid polyarthritis with vascular involvement and review of the literature. *Ann Med Interne (Paris)* 1987;138:566–587. [PubMed: 2835922]
13. Genta MS, Genta RM, Gabay C. Systemic rheumatoid vasculitis: a review. *Semin Arthritis Rheum* 2006;36:88–98. [PubMed: 17023257]
14. Ward MM. Decreases in rates of hospitalizations for manifestations of severe rheumatoid arthritis, 1983–2001. *Arthritis Rheum* 2004;50:1122–1131. [PubMed: 15077294]
15. Watts RA, Lane SE, Scott DG. Decrease over time in the incidence of systemic rheumatoid vasculitis: comment on the article by Turesson et al. *Arthritis Rheum* 2005;52:1620–1621. author reply 1621. [PubMed: 15880813]
16. Watts RA, Mooney J, Lane SE, Scott DG. Rheumatoid vasculitis: becoming extinct? *Rheumatology* 2004;43:920–923. [PubMed: 15126674]
17. 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;50:3729–3731. [PubMed: 15529357]
18. Turesson C, Jacobsson L, Bergstrom U. Extra-articular rheumatoid arthritis: prevalence and mortality. *Rheumatology* 1999;38:668–674. [PubMed: 10461483]
19. Turesson C, O’Fallon WM, Crowson CS, et al. Occurrence of extraarticular disease manifestations is associated with excess mortality in a community based cohort of patients with rheumatoid arthritis. *J Rheumatol* 2002;29:62–67. [PubMed: 11824973]
20. Puechal X, Said G, Hilliquin P, et al. Peripheral neuropathy with necrotizing vasculitis in rheumatoid arthritis. A clinicopathologic and prognostic study of thirty-two patients. *Arthritis Rheum* 1995;38:1618–1629. [PubMed: 7488283]
21. Caballol Pons N, Montala N, Valverde J, et al. Isolated cerebral vasculitis associated with rheumatoid arthritis. *Joint Bone Spine* 2010;77:361–363. [PubMed: 20471884]
22. Zolcinski M, Bazan-Socha S, Zwolinska G, Musial J. Central nervous system involvement as a major manifestation of rheumatoid arthritis. *Rheumatol Int* 2008;28:281–283. [PubMed: 17690887]
23. Chen KR, Toyohara A, Suzuki A, Miyakawa S. Clinical and histopathological spectrum of cutaneous vasculitis in rheumatoid arthritis. *Br J Dermatol* 2002;147:905–913. [PubMed: 12410699]
24. Voskuyl AE, Hazes JM, Zwinderman AH, et al. Diagnostic strategy for the assessment of rheumatoid vasculitis. *Ann Rheum Dis* 2003;62:407–413. [PubMed: 12695150]
25. Coremans IE, Hagen EC, Daha MR, et al. Antilactoferrin antibodies in patients with rheumatoid arthritis are associated with vasculitis. *Arthritis Rheum* 1992;35:1466–1475. [PubMed: 1282009]
26. Scott DG, Bacon PA. Intravenous cyclophosphamide plus methylprednisolone in treatment of systemic rheumatoid vasculitis. *Am J Med* 1984;76:377–384. [PubMed: 6142648]
27. Espinoza LR, Espinoza CG, Vasey FB, Germain BF. Oral methotrexate therapy for chronic rheumatoid arthritis ulcerations. *J Am Acad Dermatol* 1986;15:508–512. [PubMed: 3760277]
28. Upchurch KS, Heller K, Bress NM. Low-dose methotrexate therapy for cutaneous vasculitis of rheumatoid arthritis. *J Am Acad Dermatol* 1987;17:355–359. [PubMed: 3624579]
29. Segal R, Caspi D, Tishler M, et al. Accelerated nodulosis and vasculitis during methotrexate therapy for rheumatoid arthritis. *Arthritis Rheum* 1988;31:1182–1185. [PubMed: 3422015]
30. Combe B, Didry C, Gutierrez M, et al. Accelerated nodulosis and systemic manifestations during methotrexate therapy for rheumatoid arthritis. *Eur J Med* 1993;2:153–156. [PubMed: 8261056]
31. Heurkens AH, Westedt ML, Breedveld FC. Prednisone plus azathioprine treatment in patients with rheumatoid arthritis complicated by vasculitis. *Arch Intern Med* 1991;151:2249–2254. [PubMed: 1953230]
32. Puechal X, Miceli-Richard C, Mejjad O, et al. Anti-tumour necrosis factor treatment in patients with refractory systemic vasculitis associated with rheumatoid arthritis. *Ann Rheum Dis*

2008;67:880–884. [PubMed: 18037625] This article reports on a series of cases of refractory systemic rheumatoid vasculitis treated with anti-TNF therapy that were ascertained via a European survey. Among nine cases, five complete remissions and one partial remission were reported. One patient failed and two stopped treatment.

33. Armstrong DJ, McCarron MT, Wright GD. Successful treatment of rheumatoid vasculitis-associated foot-drop with infliximab. *J Rheumatol* 2005;32:759. author reply 759–760. [PubMed: 15801041]
34. Bartolucci P, Ramanoelina J, Cohen P, et al. Efficacy of the anti-TNF-alpha antibody infliximab against refractory systemic vasculitides: an open pilot study on 10 patients. *Rheumatology (Oxford)* 2002;41:1126–1132. [PubMed: 12364631]
35. Garcia-Porrua C, Gonzalez-Gay MA. Successful treatment of refractory mononeuritis multiplex secondary to rheumatoid arthritis with the anti-tumour necrosis factor alpha monoclonal antibody infliximab. *Rheumatology (Oxford)* 2002;41:234–235. [PubMed: 11886980]
36. Garcia-Porrua C, Gonzalez-Gay MA, Quevedo V. Should anti-tumor necrosis factor-alpha be the first therapy for rheumatoid vasculitis? *J Rheumatol* 2006;33:433. author reply 433–434. [PubMed: 16465676]
37. Unger L, Kayser M, Nusslein HG. Successful treatment of severe rheumatoid vasculitis by infliximab. *Ann Rheum Dis* 2003;62:587–588. [PubMed: 12759302]
38. van der Bijl AE, Allaart CF, Van Vugt J, et al. Rheumatoid vasculitis treated with infliximab. *J Rheumatol* 2005;32:1607–1609. [PubMed: 16078342]
- 39•. Ramos-Casals M, Brito-Zeron P, Munoz S, et al. Autoimmune diseases induced by TNF-targeted therapies: analysis of 233 cases. *Medicine (Baltimore)* 2007;86:242–251. [PubMed: 17632266]
This article describes a MEDLINE review of all published cases of autoimmune diseases attributed to anti-TNF agents through December 2006, including 113 reported vasculitis cases. The relative reported frequency with specific agents is discussed (etanercept, 59; infliximab, 47; adalimumab, 5; other, 2).
- 40•. Guignard S, Gossec L, Bandinelli F, Dougados M. Comparison of the clinical characteristics of vasculitis occurring during anti-tumor necrosis factor treatment or not in rheumatoid arthritis patients. A systematic review of 2707 patients, 18 vasculitis. *Clin Exp Rheumatol* 2008;26(3 Suppl 49):S23–S29. [PubMed: 18799049] This large, single-center, retrospective analysis performed a case-cohort study to examine the causal relationship between TNF treatment and vasculitis to conclude that a minority of cases could potentially be attributed to anti-TNF drugs.
- 41•. Hellmann M, Jung N, Owczarczyk K, et al. Successful treatment of rheumatoid vasculitis-associated cutaneous ulcers using rituximab in two patients with rheumatoid arthritis. *Rheumatology (Oxford)* 2008;47:929–930. [PubMed: 18411212] This brief report describes two cases of rheumatoid vasculitis ulcers successfully treated with rituximab following failure of standard DMARDs and prednisone.
42. Maher LV, Wilson JG. Successful treatment of rheumatoid vasculitis-associated foot drop with rituximab. *Rheumatology (Oxford)* 2006;45:1450–1451. [PubMed: 16936329]
43. Kim MJ, Kim HO, Kim HY, Park YM. Rituximab-induced vasculitis: a case report and review of the medical published work. *J Dermatol* 2009;36:284–287. [PubMed: 19382999]
44. Cambridge G, Stohl W, Leandro MJ, et al. Circulating levels of B lymphocyte stimulator in patients with rheumatoid arthritis following rituximab treatment: relationships with B cell depletion, circulating antibodies, and clinical relapse. *Arthritis Rheum* 2006;54:723–732. [PubMed: 16508933]
45. Jones RB, Ferraro AJ, Chaudhry AN, et al. A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2009;60:2156–2168. [PubMed: 19565480]
46. Eriksson P. Nine patients with anti-neutrophil cytoplasmic antibody-positive vasculitis successfully treated with rituximab. *J Intern Med* 2005;257:540–548. [PubMed: 15910558]
47. Keogh KA, Ytterberg SR, Fervenza FC, et al. Rituximab for refractory Wegener's granulomatosis: report of a prospective, open-label pilot trial. *Am J Respir Crit Care Med* 2006;173:180–187. [PubMed: 16224107]
48. Albano SA, Santana-Sahagun E, Weisman MH. Cigarette smoking and rheumatoid arthritis. *Semin Arthritis Rheum* 2001;31:146–159. [PubMed: 11740796]

Fig 1. Rheumatoid vasculitis leg ulcers in a 58-year-old seropositive, poorly controlled rheumatoid arthritis patient. One lesion was histologically proven, and all cleared after 4 months of treatment with azathioprine and prednisone.

Table 1

Clinical organ system involvement of rheumatoid vasculitis

System	Manifestation
Skin	Purpura, focal digital lesions, ulcers, digital necrosis, pyoderma
Peripheral nervous system	Distal sensory or motor neuropathy, mononeuritis multiplex
Eye	Corneal ulceration, scleromalacia
Pulmonary	Fibrosing alveolitis, alveolar hemorrhage
Cardiac	Myocardial infarction, cardiomyopathy
Renal	Interstitial nephritis, glomerulonephritis
Gastroenterologic	Ischemic bowel; ulcerations; arteritis of liver, spleen, pancreas
Central nervous system	Transient ischemic attack, stroke, seizure

Table 2

Therapy for rheumatoid vasculitis

Agent	Average dose
Prednisone	30–200 mg/d orally or IV
Methotrexate	10–25 mg/wk orally or IM
Azathioprine	50–150 mg/d orally
Cyclophosphamide	IV or orally, weight dosed
Anti-TNF agents	Varies by agent
Rituximab	1000 mg IV weeks 0 and 2

IM—intramuscularly; IV—intravenously; TNF—tumor necrosis factor