
Discontinuation of therapies in vasculitis

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ABSTRACT

For most patients with vasculitis, treatment will result in prevention of mortality and also lead to clinical remission. This increased survival is of course most welcome, but the burden of surviving an episode of acute vasculitis consists of the effects of the disease as well as the adverse events from treatment. Therefore, we have begun to explore the possibility of withdrawing treatment in order to avoid long-term medication toxicities. Whilst this will reduce short-term side effects, if withdrawal leads to subsequent uncontrolled flares of disease, the need for additional therapy may outweigh any benefit from a drug-free holiday. For very mild forms of vasculitis, such as isolated skin vasculitis, the best option may be to avoid treatment altogether. In those patients with vasculitis secondary to an identifiable agent such as drug toxicity or an infectious organism, discontinuing the offending drug or treating the infection will usually resolve or cure the vasculitis. In patients with localised vasculitis, surgical removal of the affected area can be curative. Other forms of vasculitis have a self-limited duration, after which there does not appear to be any clinical evidence of disease, such as is the case for the majority of patients with giant cell arteritis. By contrast, in many forms of vasculitis, especially those associated with the presence of anti-neutrophil cytoplasm antibody (ANCA), relapse occurs in at least half the patients. Where glucocorticoid therapy is used for any length of time, in doses of >5 mg/day, side effects are almost universal. Adding a concomitant agent in the attempt to shorten the course and/or reduce the dose of glucocorticoid treatment may be effective, but can also result in toxicity from the alternative agent, and leaves the patient on immunosuppressive therapy. More toxic therapy, such as cyclophosphamide, usually is administered only for a limited time or cumulative amount, in order to achieve induction of remission or flare in severe

disease. The advent of targeted biologic therapy offers the opportunity to provide more effective, less toxic and perhaps more long-lasting control of disease. Rituximab in small-vessel vasculitis can result in long-lasting control of disease, for 18 months or more, from a single course of treatment. Suppression of the interleukin-6 pathway may be effective in large-vessel vasculitis. Unfortunately, none of these therapies is capable of "cure" for the majority of patients. Therefore, discontinuation of therapy remains unachievable for most patients with vasculitis, at least in the first few years of disease. Short courses of intensive, aggressive therapy are followed by the use of maintenance treatment. Long-term follow-up studies are required to determine the potential benefit of early, more effective control of vasculitis.

What is vasculitis?

The systemic vasculitides are an uncommon set of disorders characterised by inflammation of blood vessels leading to end organ damage (1). They vary from trivial to life-threatening (2), and occur at all ages. For many forms, therapy can be organ- and life-saving (1), but is also the cause of significant morbidity (3) and in itself carries a mortality risk (2, 3). Therefore, in considering treatment for a patient with vasculitis, it is important to attempt to determine the precise need for the treatment, the quality or characteristic of the treatment, and its duration. It is also important to be able to assess treatment response quantitatively, if possible. For some patients, no treatment may be required because the condition is self-limiting, whereas in others with much more severe multi-organ disease, treatment is essential to prevent morbidity and early mortality.

What therapies are necessary to treat vasculitis?

No pharmacological therapy

In patients with small-vessel vasculitis limited to the skin, no treatment may be

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safer than treatment (4). Patients treated with colchicine had significantly more adverse events (mainly gastrointestinal toxicity) than those on placebo in a small randomised trial of isolated cutaneous vasculitis (4). Simple management such as elevating the legs and avoiding prolonged standing may reduce the burden of the disease. There is no evidence that Henoch-Schönlein purpura responds to immunosuppression, which should be avoided in most cases (5).

Glucocorticoids

Steroids on their own are effective in the management of most cases of giant cell arteritis. Typically the patient will be treated with high doses of glucocorticoids (1 mg/kg per day) on a reducing course over a period of 18–24 months to discontinue therapy (6). The risk of relapse is about 30% (7). Symptom control is usually achieved very early; by contrast, toxicity is considerable, occurring in more than 80% of patients, and may seem to outweigh the benefits (8). Steroids can be used as part of the management of other forms of vasculitis and often form the core of any treatment plan. However there is a tendency to over-use steroids, especially early on, and the evidence for a differential effect from very high doses of steroid such as 3 x 1g IV methylprednisolone, compared to smaller doses, is relatively modest. In very severe anti-neutrophil cytoplasm antibody- (ANCA-) associated vasculitis, there is no additional early benefit to IV methylprednisolone pulses on top of standard steroid therapy plus cyclophosphamide, compared to additional plasma exchange (9), although in subsequent follow-up, the distinction between the effect of plasmapheresis and methylprednisolone was less clear (10). Unfortunately, systemic features such as muscle cramps, joint pain and malaise do not respond rapidly to drugs such as cyclophosphamide, methotrexate or azathioprine. By contrast, the steroid response is often immediate. Unfortunately the burden of high-dose steroids is considerable, especially in the elderly. In a recent review of the European Vasculitis Study group cohorts of patients with primary systemic ANCA-associated vasculitis, the one-

year mortality was 11.1%, of whom 59% died because of therapy-associated events. The majority of these are likely to have been steroid-related (3).

These data raise a concern that our attempt to suppress the inflammatory response in vasculitis carries the risk of causing significant harm. Therefore efforts have been initiated to reduce the overall drug toxicity, starting with a reduction in overall steroid use. Attempts to rapidly withdraw corticosteroids in patients with giant cell arteritis by using concomitant therapy with methotrexate (11–13) were only modestly successful. Rapid withdrawal of glucocorticoids, supported by either methotrexate or tumour necrosis factor inhibitor therapy has not been successful at controlling disease (14, 15). On meta-analysis, there was at most a modest benefit from methotrexate (13). However, not all patients with a rapid steroid withdrawal regimen actually relapsed, raising the possibility that for some patients with giant cell arteritis (around 15%), a shorter course of steroid therapy might be effective, leading to permanent discontinuation. If we could identify these patients in advance, their treatment regimen could be planned to avoid excess steroid burden. In ANCA-associated vasculitis, reducing the overall use of glucocorticoid therapy carries a significant risk factor for relapse (16). Not surprisingly, therefore, there have not been any randomised controlled trials without glucocorticoid therapy to date for ANCA-associated vasculitis. Two studies currently in progress are designed to assess the potential for reducing the total steroid dose: a study assessing plasma exchange versus standard therapy in ANCA vasculitis includes a stratification for patients to receive a reduced dose of glucocorticoid (0.5 mg/kg/day), compared to 1mg/kg/day as standard therapy (PEXIVAS, <http://clinicaltrials.gov/ct2/show/NCT00987389>); the other study is looking at the role of a Complement 5a inhibitor in the management of systemic vasculitis (CLEAR, Chemocentryx, <http://www.controlled-trials.com/ISRCTN53663626>), and will be testing the effect of this compound for some patients in the absence of any glucocorticoid therapy.

Immunomodulatory therapies for vasculitis

Methotrexate, azathioprine, leflunomide, mycophenolate mofetil, ciclosporin and cyclophosphamide are amongst a number of immunosuppressive agents used to manage patients with vasculitis. Cyclophosphamide is a cytotoxic agent which revolutionised the management of small-vessel multi-system vasculitis such as the ANCA-associated vasculitides, reducing the mortality from over 80% at one year to less than 10% at 18 months (1, 17), as well as showing benefit in a small series of cases with resistant giant cell arteritis (18). However it carries considerable risk, including long-term toxicities of increased risk of bladder cancer, infertility, hair loss, and sepsis. Short courses of cyclophosphamide, for example 2 mg/kg/day orally for up to 6 months (19), can be very effective as induction regimens for systemic vasculitis followed by maintenance therapy with less toxic regimens, *e.g.* azathioprine or methotrexate (19, 20). Pulse high-dose intravenous cyclophosphamide given as 15 mg/kg on 6 to 10 occasions over three to six months as induction therapy delivers even less total cyclophosphamide than the daily oral regimen (approximately one-third less) but with similar achievement of remission, and allowing for the possibility of a repeat course of treatment if the patient relapses (21, 17). Although it is not clear what the upper limit of safety of cyclophosphamide is, it has been suggested that cumulative doses below 35 g are safer than those above this level (22, 23), especially in terms of cancer risk.

On the other hand, relapse is a major concern for patients with vasculitis, occurring in about 50% of patients with ANCA-associated vasculitis (24) and potentially causing further end-organ damage, and increasing mortality risk in some (25), but not all (17), studies. Therefore, it is not always obvious what is in the best interest of the individual patient: is it better to use less cyclophosphamide with an increased risk of relapse, which can be treated if necessary with more cyclophosphamide – or should the patient be exposed to more cyclophosphamide to reduce

the risk of relapse, thereby inevitably increasing the long-term potential toxicity from cyclophosphamide?

Methotrexate has been used in patients with localised granulomatosis with polyangiitis (GPA) (26). However, it has been suggested that patients receiving methotrexate have a much higher risk of relapse, and of a subsequent need to switch to cyclophosphamide (27). However, these data are based on a study of patients randomised to receive twelve months of steroids plus either methotrexate or cyclophosphamide for treatment of localised GPA, after which all therapies were discontinued. Most patients subsequently relapsed. If patients had been allocated to longer-term methotrexate therapy – *i.e.* for at least 3 or 4 years – it is possible that the results would have been different. After all, rheumatologists are experienced in managing patients with chronic inflammatory diseases, particularly rheumatoid arthritis, with long-term methotrexate therapy, with evidence that 80% continued methotrexate for 5 years (28). There are limited data concerning methotrexate in Takayasu arteritis; it was the most commonly used concomitant immunosuppressive agent used in a large cohort of patients from Turkey (29), but there are no controlled trials. Mycophenolate mofetil appears to have similar efficacy to cyclophosphamide for induction of remission in ANCA-associated vasculitis (30), but appears inferior to azathioprine for maintenance (31). A very small open label study of mycophenolate mofetil showed benefit in 10 patients with Takayasu arteritis (32). Azathioprine has been used for many years as a maintenance agent for systemic vasculitis (19). In one trial, high-dose azathioprine was effective as induction therapy for patients who failed to respond to cyclophosphamide for systemic vasculitis (33). Trials of leflunomide are confined to patients who had granulomatosis with polyangiitis and only localised disease; very high doses (up to 40 mg/day) can induce remission and are superior to methotrexate for maintenance, but cause more adverse events (34, 35).

Specific, targeted therapies are available for some forms of vasculitis. In

Kawasaki disease, the treatment is with high dose of intravenous immunoglobulin (IVIG) and high doses of aspirin for 5 days, following which all therapies are discontinued (36). In resistant cases, some additional steroid therapy might be used, but this is controversial. In one study, a single large dose of steroid made no difference to the outcome (37), whilst a more recent study of 15 days of regular steroids 2 mg/kg in addition to IVIG reduced coronary artery complications significantly (38). Kawasaki disease appears to be a “one-shot” condition in most cases. However, there are reports of premature cardiovascular events in adults who suffered the disease in childhood, regardless of whether or not they had developed coronary artery aneurysms during the acute illness (39).

Long-term use of IVIG in ANCA-associated vasculitis is limited by expense and potential hazards (such as hepatitis C contamination in the early days). It has the potential to modulate immunological reactions and has successfully been used for therapy in severe vasculitis, but its effects are temporary (40, 41). Specific targeting of B cells by rituximab may be an effective regimen in ANCA-associated vasculitis (42, 43, 44) and in cryoglobulinaemic vasculitis (45). However, B cell depletion is temporary and therefore re-population of these cells often leads to recrudescence of the underlying disease (46).

Limited data are available concerning the benefit of guselimumab, a less toxic immunosuppressive agent, in controlling resistant cases of granulomatosis with polyangiitis (47, 48), but this therapy has been shown to be associated with relapse of disease on discontinuation, and therefore long-term maintenance would be required.

Conclusions

The natural history of different forms of vasculitis provides a rationale to decide the duration of therapy. For self-limiting forms of vasculitis, supportive therapy to limit damage and prevent mortality or organ failure should be followed by complete discontinuation of therapy very rapidly, as is the case for Kawasaki disease. Similarly, when vasculitis

is secondary to an infectious insult (49) (*e.g.* streptococcal-related rheumatic fever, bacterial endocarditis, hepatitis B (50)) or chemical insult (*e.g.* cocaine- (51) or levamisole-induced vasculitis (52)), then treatment of the organism or discontinuation of the chemical is the main therapeutic intervention, although temporary immunosuppression may be required. By contrast, other viral infections associated with vasculitis such as hepatitis C are more difficult to eradicate and therefore on-going therapy is likely to be needed, both for the manifestations of the vasculitis as well as for controlling the viral load. Giant cell arteritis is relapsing in up to a third of individuals (53). Takayasu arteritis has a very long natural history and leads to irreversible ischaemia, if untreated (54). ANCA-associated vasculitis has a mortality of over 85% if untreated, and the natural history of treated ANCA vasculitis suggests that at least 50% of patients will relapse between 5 and 10 years from diagnosis (1). It seems unlikely that discontinuation of therapy is a feasible option for most patients with primary vasculitis until we have a better understanding of the underlying pathophysiologic mechanisms so that they can be directly targeted.

References

1. BERDEN A, GÖÇEROĞLU A, JAYNE D *et al.*: Diagnosis and management of ANCA associated vasculitis. *BMJ* 2012; 344: e26.
2. PHILLIP R, LUQMANN R: Mortality in systemic vasculitis: a systematic review. *Clin Exp Rheumatol* 2008; 26 (Suppl. 51): S94-104.
3. LITTLE MA, NIGHTINGALE P, VERBURGH CA *et al.*: EUROPEAN VASCULITIS STUDY (EUVAS) GROUP: Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis. *Ann Rheum Dis* 2010; 69: 1036-43.
4. SAIS G, VIDALLER A, JUCGLÀ A, GALLARDO F, PEYRÍ J: Colchicine in the treatment of cutaneous leukocytoclastic vasculitis. Results of a prospective, randomized controlled trial. *Arch Dermatol* 1995; 131: 1399-402.
5. JAUHOLA O, RONKAINEN J, KOSKIMIES O *et al.*: Outcome of Henoch-Schönlein purpura 8 years after treatment with a placebo or prednisone at disease onset. *Pediatr Nephrol* 2012; 27: 933-9.
6. SPIERA RF, MITNICK HJ, KUPERSMITH M *et al.*: A prospective, double-blind, randomized, placebo controlled trial of methotrexate in the treatment of giant cell arteritis (GCA). *Clin Exp Rheumatol* 2001; 19: 495-501.
7. VISVANATHAN S, RAHMAN MU, HOFFMAN GS *et al.*: Tissue and serum markers of in-

- flammation during the follow-up of patients with giant-cell arteritis—a prospective longitudinal study. *Rheumatology* (Oxford) 2011; 50: 2061-70.
8. PROVEN A, GABRIEL SE, ORCES C, O'FALLON WM, HUNTER GG: Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. *Arthritis Rheum* 2003; 49: 703-8.
 9. JAYNE DR, GASKIN G, RASMUSSEN N *et al.*; EUROPEAN VASCULITIS STUDY GROUP: Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol* 2007; 18: 2180-8.
 10. WALSH M, CASIAN A, FLOSSMANN O *et al.*: Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear. *Kidney Int* 2013; 84: 397-402.
 11. JOVER JA, HERNÁNDEZ-GARCÍA C, MORADO IC, VARGAS E, BAÑARES A, FERNÁNDEZ-GUTIÉRREZ B: Combined treatment of giant-cell arteritis with methotrexate and prednisone. a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2001; 134: 106-14.
 12. HOFFMAN GS, CID MC, HELLMANN DB *et al.*; INTERNATIONAL NETWORK FOR THE STUDY OF SYSTEMIC VASCULITIDES: A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. *Arthritis Rheum* 2002; 46: 1309-18.
 13. MAHR AD, JOVER JA, SPIERA RF *et al.*: Adjunctive methotrexate for treatment of giant cell arteritis: an individual patient data meta-analysis. *Arthritis Rheum* 2007; 56: 2789-97.
 14. HOFFMAN GS, CID MC, RENDT-ZAGAR KE *et al.*; INFLIXIMAB-GCA STUDY GROUP: Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomized trial. *Ann Intern Med* 2007 May; 146: 621-30.
 15. SEROR R, BARON G, HACHULLA E *et al.*: Adalimumab for steroid sparing in patients with giant-cell arteritis: results of a multicenter randomised controlled trial. *Ann Rheum Dis* 2013 Jul 29.
 16. WALSH M, MERKEL PA, MAHR A, JAYNE D: Effects of duration of glucocorticoid therapy on relapse rate in antineutrophil cytoplasmic antibody-associated vasculitis: A meta-analysis. *Arthritis Care Res* (Hoboken) 2010; 62: 1166-73.
 17. HARPER L, MORGAN MD, WALSH M *et al.*; EUVAS INVESTIGATORS: Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. *Ann Rheum Dis* 2012; 71: 955-60.
 18. DE BOYSSON H, BOUTEMY J, CREVEUIL C *et al.*: Is there a place for cyclophosphamide in the treatment of giant-cell arteritis? A case series and systematic review. *Semin Arthritis Rheum* 2013; 43: 105-12.
 19. JAYNE D, RASMUSSEN N, ANDRASSY K *et al.*; EUROPEAN VASCULITIS STUDY GROUP: A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med* 2003; 349: 36-44.
 20. PAGNOUX C, MAHR A, HAMIDOU MA *et al.*; FRENCH VASCULITIS STUDY GROUP: Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. *N Engl J Med* 2008; 359: 2790-803.
 21. DE GROOT K, HARPER L, JAYNE DR *et al.*; EUVAS (EUROPEAN VASCULITIS STUDY GROUP): Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med* 2009; 150: 670-80.
 22. TALAR-WILLIAMS C, HIJAZI YM, WALTHER MM *et al.*: Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener granulomatosis. *Ann Intern Med* 1996; 124: 477-84.
 23. ZYCINSKA K, KOSTRZEWA-JANICKA J, NITSCH-OSUCH A, WARDYN K: Cancer incidence in pulmonary vasculitis. *Adv Exp Med Biol* 2013; 788: 349-53.
 24. WALSH M, FLOSSMANN O, BERDEN A *et al.*; EUROPEAN VASCULITIS STUDY GROUP: Risk factors for relapse of antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2012; 64: 542-8.
 25. DE JOODE AA, SANDERS JS, STEGEMAN CA: Renal Survival in Proteinase 3 and Myeloperoxidase ANCA-Associated Systemic Vasculitis. *Clin J Am Soc Nephrol* 2013. [Epub ahead of print]
 26. 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.
 27. FAURSCHOU M, WESTMAN K, RASMUSSEN N *et al.*; EUROPEAN VASCULITIS STUDY GROUP: Brief Report: long-term outcome of a randomized clinical trial comparing methotrexate to cyclophosphamide for remission induction in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2012; 64: 3472-7.
 28. YAZICI Y, SOKKA T, KAUTIAINEN H, SWEARINGEN C, KULMAN I, PINCUS T: Long term safety of methotrexate in routine clinical care: discontinuation is unusual and rarely the result of laboratory abnormalities. *Ann Rheum Dis* 64; 207-11.
 29. BICAKCIGIL M, AKSU K, KAMALI S *et al.*: Takayasu's arteritis in Turkey - clinical and angiographic features of 248 patients. *Clin Exp Rheumatol* 2009; 27 (Suppl. 52): S59-64.
 30. HU W, LIU C, XIE H, CHEN H, LIU Z, LI L: Mycophenolate mofetil versus cyclophosphamide for inducing remission of ANCA vasculitis with moderate renal involvement. *Nephrol Dial Transplant* 2008; 23: 1307-12. Epub 2007 Dec 8.
 31. HIEMSTRA TF, WALSH M, MAHR A *et al.*; EUROPEAN VASCULITIS STUDY GROUP (EUVAS): Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. *JAMA* 2010; 304: 2381-8.
 32. SHINJO SK, PEREIRA RM, TIZZIANI VA, RADU AS, LEVY-NETO M: Mycophenolate mofetil reduces disease activity and steroid dosage in Takayasu arteritis. *Clin Rheumatol* 2007; 26: 1871-5.
 33. ARIES PM, HELLMICH B, REINHOLD-KELLER E, GROSS WL: High-dose intravenous azathioprine pulse treatment in refractory Wegener's granulomatosis. *Rheumatology* (Oxford) 2004; 43: 1307-8.
 34. METZLER C, FINK C, LAMPRECHT P, GROSS WL, REINHOLD-KELLER E: Maintenance of remission with leflunomide in Wegener's granulomatosis. *Rheumatology* (Oxford) 2004; 43: 315-20.
 35. METZLER C, MIEHLE N, MANGER K *et al.*; GERMAN NETWORK OF RHEUMATIC DISEASES: Elevated relapse rate under oral methotrexate versus leflunomide for maintenance of remission in Wegener's granulomatosis. *Rheumatology* (Oxford) 2007; 46: 1087-91.
 36. NEWBURGER JW, TAKAHASHI M, BURNS JC *et al.*: The treatment of Kawasaki syndrome with intravenous gamma globulin. *N Engl J Med* 1986; 315: 341-7.
 37. NEWBURGER JW, SLEEPER LA, MCCRINDLE BW *et al.*; PEDIATRIC HEART NETWORK INVESTIGATORS: Randomized trial of pulsed corticosteroid therapy for primary treatment of Kawasaki disease. *N Engl J Med* 2007; 356: 663-75.
 38. KOBAYASHI T, SAJI T, OTANI T *et al.*; RAISE STUDY GROUP INVESTIGATORS: Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial. *Lancet* 2012; 379: 1613-20.
 39. ZANON G, ZUCCHETTA P, VARNIER M, VITTADELLO F, MILANESI O, ZULIAN F: Do Kawasaki disease patients without coronary artery abnormalities need a long-term follow-up? A myocardial single-photon emission computed tomography pilot study. *J Paediatr Child Health* 2009; 45: 419-24.
 40. MARTINEZ V, COHEN P, PAGNOUX C *et al.*; FRENCH VASCULITIS STUDY GROUP: Intravenous immunoglobulins for relapses of systemic vasculitides associated with antineutrophil cytoplasmic autoantibodies: results of a multicenter, prospective, open-label study of twenty-two patients. *Arthritis Rheum* 2008; 58: 308-17.
 41. JAYNE DR, CHAPEL H, ADU D *et al.*: Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. *QJM* 2000; 93: 433-9.
 42. JONES RB, TERVAERT JW, HAUSER T *et al.*; EUROPEAN VASCULITIS STUDY GROUP: Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med* 2010; 363: 211-20.
 43. STONE JH, MERKEL PA, SPIERA R *et al.*; RAVE-ITN RESEARCH GROUP: Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010; 363: 221-32.
 44. Specks U, Merkel PA, Seo P, *et al.*; RAVE-ITN RESEARCH GROUP: Efficacy of remission-induction regimens for ANCA-associated vasculitis. *N Engl J Med* 2013; 369: 417-27.
 45. DE VITA S, QUARTUCCIO L, ISOLA M *et al.*: A randomized controlled trial of rituxi-

- mab for the treatment of severe cryoglobulinemic vasculitis. *Arthritis Rheum* 2012; 64: 843-53.
46. SMITH KG, JONES RB, BURNS SM, JAYNE DR: Long-term comparison of rituximab treatment for refractory systemic lupus erythematosus and vasculitis: Remission, relapse, and re-treatment. *Arthritis Rheum* 2006; 54: 2970-82.
 47. BIRCK R, WARNATZ K, LORENZ HM *et al.*: 15-Deoxyspergualin in patients with refractory ANCA-associated systemic vasculitis: a six-month open-label trial to evaluate safety and efficacy. *J Am Soc Nephrol* 2003; 14: 440-7.
 48. FLOSSMANN O, BASLUND B, BRUCHFELD A *et al.*: Deoxyspergualin in relapsing and refractory Wegener's granulomatosis. *Ann Rheum Dis* 2009; 68: 1125-30.
 49. SCHENA FP: Survey of the Italian Registry of Renal Biopsies. Frequency of the renal diseases for 7 consecutive years. The Italian Group of Renal Immunopathology. *Nephrol Dial Transplant* 1997; 12: 418-26.
 50. GUILLEVIN L, MAHR A, COHEN P *et al.*; FRENCH VASCULITIS STUDY GROUP: Short-term corticosteroids then lamivudine and plasma exchanges to treat hepatitis B virus-related polyarteritis nodosa. *Arthritis Rheum* 2004; 51: 482-7.
 51. LUTFY J, NOLAND ME, JARMUSKE M: How to spot cocaine-induced pseudovasculitis. *Ann Plast Surg* 2013; 70: 375-8.
 52. GROSS RL, BRUCKER J, BAHCE-ALTUNTAS A *et al.*: A novel cutaneous vasculitis syndrome induced by levamisole-contaminated cocaine. *Clin Rheumatol* 2011; 30: 1385-92.
 53. VISVANATHAN S, RAHMAN MU, HOFFMAN GS *et al.*: Tissue and serum markers of inflammation during the follow-up of patients with giant-cell arteritis--a prospective longitudinal study. *Rheumatology (Oxford)* 2011; 50: 2061-70.
 54. ISHIKAWA K, MAETANI S: Long-term outcome for 120 Japanese patients with Takayasu's disease. Clinical and statistical analyses of related prognostic factors. *Circulation* 1994; 90: 1855-60.