Roadmap to vasculitis: a rheumatological treasure hunt

Part IV. Management of vasculitis

YT Konttinen[1,2,3], T Pettersson[1], M Matucci-Cerinic[4], J Dadoniene[5], P Poduval[1]

ABSTRACT

At the stop sign we read the "red flags" and made up our mind and followed one of the road signs pointing to secondary, primary or fake vasculitis. Since then we have steadily followed the road map and passed the first (patient history and physical exam), second and third milestones (laboratory, imaging and pathology studies in the primary care and specialized centres) and have finally reached our destination at the fourth milestone (Part IV) on the road map review to vasculitis. In the management of these syndromes, Birmingham Vasculitis Activity Score (BVAS) and Vasculitis Damage Index (VDI) are not widely used in the routine clinical work, but they are introduced as the idea behind them is really valid. The backbone of the medical therapy is the use of immunosuppressive doses of prednisone (1 mg/kg/day). In some life-threatening and non-responsive vasculitides this is combined with cyclophosphamide 2–4 mg/kg/day or 0.5–1.0 g/m^2 i.v. every 2–4 weeks (European Vasculitis group uses 15 mg/kg every 2–3 weeks), often at 3–6 months substituted either with methotrexate or azathioprine. In contrast, i.v. immunoglobulins are to be used in Kawasaki's syndrome; cyclosporine, dapsone or colchicine in Behçet's disease; calcium channel blockers in BACNS; and NSAID in small vessel disease; whereas plasmapheresis or immunoadsorption are added to the therapy in Goodpasture's syndrome. Particular attention is drawn to the treatment of the triggers, use of biologicals and new cytostatic drugs and anti-metabolites, prevention of thromboembolic complications with anti-platelet drugs as well as to odd and orphan entities. A short travelogue ends our odyssey as the last sign on our roadmap.

DESTINATION (FOURTH MILESTONE): MANAGEMENT OF VASCULITIS

Disease activity and damage indices (BVAS and VDI)

In the hospital, the activity and extent of vasculitis is examined. This is important for the justification of the use of potentially harmful immunosuppressive treatment. Structured instruments such as the Birmingham Vasculitis Activity Score[1] (BVAS scores can range from 0 to 67, with higher scores indicating more active disease) and the Vasculitis Damage Index[2] (VDI) are useful in this respect. The activity index BVAS was developed based on an intention to treat vasculitis with immunosuppressive therapy. It is based on nine different organ systems, all of which have a ceiling effect, the so-called maximum total so that no organ system can be overemphasized at the cost of the others. All manifestations are scored only if the changes are considered to be caused by an active vasculitis. Some tests, like von Willebrand factor or procalcitonin, can, perhaps in the future, provide help in the assessment of the general vasculitic disease activity.

In contrast, damage, either present or absent, is defined as the presence of irreversible scars of at least 3 months duration which have developed since the onset of vasculitis. The VDI score contains 64 items of damage, including five items of repeat episodes of damage (myocardial infarction

[1]Department of Medicine/invärtes medicin, Helsinki University Central Hospital, [2]ORTON Orthopaedic Hospital of the Invalid Foundation, Helsinki, [3]COXA Hospital for Joint Replacement, Tampere, Finland, [4]Department of Medicine, University of Florence, Florence, Italy, [5]Institute of Experimental & Clinical Medicine, Vilnius University, Vilnius, Lithuania.
Correspondence: *Dr. YT Konttinen, email: yrjo.konttinen@helsinki.fi*

and a second episode, absent peripheral pulse in one limb and a second episode, major tissue loss and a second episode, blindness first in one and then in the other eye, a cerebrovascular accident and a second episode), and one item to record any other damage that is not scored. They enable the clinician to differentiate active disease from irreversible but stable damage. In many centres vasculitis patients are enrolled into international controlled clinical trials on the treatment of vasculitis where these indices are commonly used.

Management of vasculitis

If and when the triggering and perpetuating factor cannot be identified, the management of primary vasculitis is based on immunosuppression (Table 1).[3] Immunosuppression is also used in the management of secondary vasculitis with poor response to treatment targeted at the elimination of the suspected triggering factor.[4] Treatment is to some extent experimental and individualised, but some evidence-based management strategies do exist. The aims are induction and maintenance of remission, improvement in survival and reduction of disease-related morbidity.

Large vessel vasculitis

In large-vessel vasculitis, treatment is initiated with prednisolone 40–60 mg/day (Table 1). Inflammatory musculoskeletal symptoms and accompanying polymyalgia rheumatica disappear rapidly upon initiation of prednisolone. Therapeutic response provides support to the preliminary diagnosis. In temporal arteritis, treatment has to be, due to the risk of blindness and other complications, commenced immediately when the diagnosis is suspected.[5] If the patient has ocular symptoms, treatment is initiated with methylprednisolone pulses given intravenously. In spite of the excellent subjective treatment response of the inflammatory component of the giant cell arteritis during short-term treatment, the immune-inflammation of the vessel wall can gradually undermine this benefit in long-term treatment, usually over decades, and lead to aortic aneurysms, aortic valve insufficiency and anastomotic aneurysms in surgically treated cases. This raises questions about the optimal length of the treatment. Due to the iatrogenic long-term complications of glucocorticoids, steroid-sparing medication should be considered. Presently in Takayasu arteritis, azathioprine[6] or weekly methotrexate[7] seem to be able to add to the efficacy and enable tapering of the glucocorticoids.[8] In temporal

Table 1 Anti-inflammatory, immunosuppressive and other systemic treatment of vasculitic diseases

Takayasu arteritis	Glucocorticoid[a]
Temporal arteritis	Glucocorticoid[a]
Behçet's disease	Glucocorticoid,[a] cyclophosphamide,[b] chlorambucil, azathioprine, cyclosporine, colchicine, thalidomide[c]
Polyarteritis nodosa	Glucocorticoid,[a] cyclophosphamide[b]
Kawasaki disease	Intravenous immunoglobulins
Bürger's disease	Smoking cessation, intravenous prostacyclin analogues
Wegener's granulomatosis	Glucocorticoid,[a] cyclophosphamide,[b] (azathioprine),[d] (plasmapheresis)[e]
Microscopic polyangiitis	Glucocorticoid,[a] cyclophosphamide,[b] (azathioprine),[d] (plasmapheresis)[e]
Churg–Straüss syndrome	Glucocorticoid,[a] cyclophosphamide,[b] (azathioprine)[d]
Primary angiitis of the central nervous system	Glucocorticoid,[a] cyclophosphamide[b] or calcium channel blockers[f]
Henoch–Schönlein purpura	NSAID,[g] dapsone, glucocorticoid,[h] (cytotoxic drugs)[h]
Essential cryoglobulinaemic vasculitis	NSAID,[g] dapsone, glucocorticosteroid,[h] (cytotoxic drugs),[h] (plasmapheresis)[e]
Leucocytoclastic vasculitis of the skin	NSAID,[g] dapsone, (glucocorticoid),[h] (cytotoxic drugs)[h]
Panniculitis	Elimination or treatment of the causative factor, anti-inflammatory drugs, cold wrappings, (glucocorticoid),[h] (cytotoxic drugs)[h]

[a]An immunosuppressive prednisolone dose is 1 mg/kg/day.

[b]Cyclophosphamide dose is 2–4 mg/kg/day or 0.5–1.0 g/m^2 intravenously every 2–4 weeks (European Vasculitis group uses 15 mg/kg every 2–3 weeks); used in patients with bad prognostic signs (for treatment of hepatitis B related polyarteritis nodosa, see text).

[c]In the treatment of arthritis and mucosal or skin changes, cyclosporine also in the treatment of uveitis.

[d]Cytotoxic drugs are used during the maintenance phase in this and other vasculitic diseases as glucocorticoid-sparing drugs.

[e]In crisis situations.

[f]Cyclophosphamide can be combined with glucocorticoids in a severe granulomatous form of the condition and calcium blockers in the milder, benign forms.

[g]As a symptomatic drug, anti-inflammatory drug (non-steroidal anti-inflammatory drug, NSAID).

[h]In severe and recurrent cases.

arteritis, azathioprine or methotrexate[9] are occasionally added to the glucocorticoid treatment as a glucocorticoid-sparing agent, but the value of this strategy is not supported by the currently available evidence.[10] Infliximab has shown some preliminary efficacy as an adjunct in the treatment of Takayasu arteritis[11] and as an initial monotherapy in temporal arteritis,[12] which is consistent with its effectiveness in Crohn's disease (another granulomatous disease). These observations need to be confirmed by controlled clinical trials, but treatment can be useful in individuals unresponsive to or intolerant of conventional glucocorticoid and/or conventional steroid-sparing agents.

In established lesions, aortic valve replacement for aortic regurgitation, repair or prosthetic replacement for aortic aneurysms and percutaneous transluminal angioplasties with stenting and endovascular atheromectomies or open endarterectomies, patch angioplasties or bypass operations (revascularisation) for occluded arteries may be required.

To prevent glucocorticosteroid-induced osteoporosis, daily intake of 1000–2000 mg calcium and 200–400 IU vitamin D should be ensured and as the treatment with glucocorticosteroid will continue over 3 months, risedronate (5 mg per day or, alternatively, 35 mg once per week) or alendronate (10 mg per day or, alternatively 70 mg once per week) should be initiated to prevent osteoporosis.

Vasculitis of medium-sized arteries

Treatment of vasculitis of the medium- and small-sized arteries in severely ill patients comprises the use of prednisolone combined with cyclophosphamide, either orally (more effective) or intravenously (safer).[3,13] This is true for polyarteritis nodosa and Churg–Straüss syndrome patients who have disease in their vital organs and display one or more bad prognostic signs in the "five-factor score". The latter takes into consideration, significant proteinuria (> 1 g/day), renal insufficiency (serum creatinine > 140 μmol/l), cardiomyopathy, gastrointestinal tract involvement and central nervous system involvement.[14] The immunosuppressant dosage is adjusted such that the blood leukocytes remain over 3.0–3.5×10^9/l and the neutrophils over 1.0–1.5×10^9/l. To avoid urinary bladder irritation and cancer, fluid intake should be at least 3 l/day, perhaps combined with the prophylactic use of mesna. In not so severely ill patients without any bad prognostic signs or in patients with hepatitis B,[15] treatment with prednisolone alone, without cyclophosphamide, may suffice. In hepatitis B carriers this should be supplemented with antiviral agents (to decrease antigen load, see below), which can be combined with plasmapheresis (to remove immune complexes) in refractory cases.

The main exception to this general rule on the use of glucocorticoids without or with cyclophosphamide is the Kawasaki disease in children, where glucocorticoids should not be used. The vasculitic plaques of the coronary arteries in children may be further weakened (catabolic effects) and thrombosed (prothrombotic effects) as a result of glucocorticosteroid treatment. This increases the risk of ruptures, bleeding, ischaemia and thromboembolic complications. In the hospital, anti-inflammatory treatment is provided, but the basic treatment comprises intravenous immunoglobulins (2 g/kg, up to 70 g) in one dose.[16] It seems unnecessary to follow the old practice of using acetylsalicylic acid in high doses (80–100 mg/kg/day as were used in North America) or medium doses (30–50 mg/kg/day as were used in Japan) in these children. Low-dose acetylsalicylic acid is used in thrombocytosis as a prophylaxis.

Vasculitis of the small arteries (ANCA-associated vasculitides)

Immunosuppression with a combination of glucocorticoids and cyclophosphamide is the mainstay of treatment for AAV.

As the use of cyclophosphamide is limited by toxicity, it has been compared to methotrexate in an unblinded, prospective, randomized, controlled trial. At 6 months, the remission rate in patients treated with prednisolone + methotrexate was not inferior (89.8%) to that seen in patients treated with prednisolone + cyclophosphamide (93.5%, $P = 0.041$). However, the prednisolone–methotrexate regimen was less effective in extensive and pulmonary disease, and associated with higher relapse rates. Maintenance beyond 12 months was recommended.[17]

When patients are treated with cyclophosphamide, it is often substituted either with methotrexate or azathioprine after 3–6 months of use to avoid long-term adverse events as has been documented in AAV.[18,19] Etanercept was not effective in the maintenance of remission in Wegener's granulomatosis, consistent with its ineffectiveness in Crohn's disease (another granulomatous disease). Its combined use with cyclophosphamide was associated with an increased risk for solid cancers.[20] Infliximab induced remission in 88% of ANCA-associated vasculitis, but 21% of the patients suffered from severe infections and 20% experienced relapses in spite of an initial response.[21] In contrast, remission of Wegener's granulomatosis was achieved by depletion of the CD20-positive B cells (plasma cell precursors) with the use of rituximab and maintained while B cells were absent encouraging further studies.[22] This approach may not work so well if instead of high ANCA titres and active vasculitis the disease is characterized by granulomas and lung nodules.[23] As an adjunct to the regular prednisone and cyclophosphamide (switched at 3 months to azathioprine), plasma exchange and methylprednisolone pulses were compared in AAV with severe renal disease (serum creatinine > 500 μmol/l,

oliguria or dialysis expected within the next 48 hours) in the MEPEX study. Patients with Churg–Sträuss syndrome obtained a good medium-term outcome when prednisone and cyclophosphamide was combined with synchronized cycles of plasmapheresis and intravenous immunoglobulin.[24]

Treatment of small-vessel vasculitis

Henoch-Schönlein purpura and cryoglobulinemia patients with general symptoms, abdominal pain and renal involvement should be sent to hospital for follow up. Intravenous infusion may be needed, and fluid and electrolyte balance and hypertension should be checked and controlled. In general, in the symptomatic treatment of small-vessel vasculitides of arterioles, capillaries and venules anti-inflammatory treatment with NSAIDs (in palpable purpura) or antihistamines (in urticaria) may suffice. Dapsone has some non-antimicrobial effects on neutrophils, which can be useful in leucocytoclastic vasculitis. More severe or recurring leukocytoclastic vasculitis (e.g. persistent nephrotic syndrome, rapidly progressive, crescentic glomerulonephritis, severe abdominal pain and bleeding) may require anti-inflammatory or even immunosuppressive doses of glucocorticoids; occasionally even cytotoxic drugs, such as azathioprine or cyclophosphamide[25] may be administered to down-regulate antibody synthesis and immune complex formation. High-dose intravenous pulse methylprednisolone together with azathioprine or cyclophosphamide have been used in severe nephritis,[26] but no controlled studies have been performed. Cryoglobulinemia, which leads to hyperviscosity syndrome, requires plasmapheresis treatment combined with chemotherapy of the underlying malignancy.

Treatment of the triggers

Triggering factors have also been identified in the so-called primary vasculitic diseases. Immunosuppression in the treatment of polyarteritis nodosa associated with hepatitis B virus can enhance viral replication and lead to cirrhosis and other complications in the long run. Lamivudine or interferon-α are therefore used in the treatment of hepatitis B-associated polyarteritis nodosa to decrease the viral antigen load after a short 2-week course on prednisone to control the vasculitis.[15] This treatment can be combined with plasmapheresis to remove immune complexes. Ribavirin and interferon-α can be used in hepatitis C-associated cryoglobulinaemic vasculitis and often lead to viral eradication and correction of the cryoglobulinemia and hypocomplementemia.[27] Combination of trimethoprim and sulfamethoxazol is used in Wegener's granulomatosis to help maintain remission and nasal mupirocin for the eradication of *Staphylococcus aureus*. Henoch–Schönlein purpura develops after approximately 3 weeks latency and usually the triggering

infection has already subsided during such time. The so-called banal infections should be rapidly and effectively diagnosed and treated in vasculitis patients on immunosuppressive drugs. The initial treatment in vasculitis often also includes empiric treatment with antimicrobial drugs.

Vasculitis and thromboembolism

Vasculitis is *per se* associated with an increased risk for arterial thrombosis and emboli as a result of inflammatory endothelial lesions in arteries. This endothelial injury exposes subendothelial collagen molecules, which initiate platelet adhesion, i.e. initiates the formation of "a white thrombus". This platelet adhesion and aggregation is inhibited in atherosclerotic and vasculitic plaques by endothelial cell-derived prostacyclin PGI_2 produced by cycloxygenase-2 (COX-2). Prednisolone inhibits the production of the inducible COX-2 and the ability of the inflamed endothelial cells to synthesize anti-thrombotic prostacyclin PGI_2. Platelets are not affected by prednisolone. They contain constitutively expressed cycloxygenase-1 (COX-1) produced already during the megakaryocyte stage of development and are able to produce pro-thrombotic thromboxane A_2 (TxA_2) even in the presence of prednisolone to promote platelet aggregation. Therefore, the use of glucocorticoids shifts the endothelial cell–platelet balance into a pro-thrombotic direction.

This can be counteracted by a low dose acetylsalicylic acid. Acetylsalicylic acid is a direct and irreversible COX inhibitor, which permanently blocks platelet COX-1 for their full 7–10 day long lifetime. Mini-ASA also blocks constitutive COX-1 and induced COX-2 in endothelial cells, but as it is used in low doses and beacuse endothelial cells like nuclear cells recover from the mini-ASA effect via *de novo* COX sythesis, mini-ASA can be used as an anti-thrombotic agent. Indeed, it has been reported that a small dose acetylsalicylic acid used in the primary or secondary prophylaxis against coronary heart disease protects against sudden loss of vision and cerebrovascular accidents in temporal arteritis.[28]

Venous thrombosis is usually associated with infections, immobilisation and activation of the coagulation cascade. Vasculitis patients should be advised to do exercises to prevent deep venous thrombosis. Thrombophlebitis may be cured by the removal of intravenous cannulae. If a vasculitis patient develops thrombosis, its medical treatment must be tailor-made individually.

Odd entities and orphan treatments

In Bürger's disease, smoking must be stopped. Calcium channel blockers and prostacyclin analogues can be used to avoid amputations. In the treatment of Behçet's disease not only cyclosporine, but dapsone and colchicine also have a place. In PACNS, granulomatous disease is treated with prednisolone

and cyclophosphamide and the benign form with calcium channel blockers. In Goodpasture's syndrome rapid diagnosis is essential as prednisolone and cyclophosphamide are necessary to suppress anti-glomerular basement membrane autoantibody production combined with plasmapheresis or immunoadsorption to remove the pathogenic autoantibodies. Management of panniculitis consists of the elimination of the triggering factor, if present and symptomatic treatment.

In life-threatening vasculitis methylprednisolone can be given as a 0.5–1.0 g/day dose on 3–5 successive days. Plasmapheresis or immunoadsorption can also be considered to facilitate the removal of immunoglobulins and immune complexes with immunoglobulin-binding protein A. Tacrolimus, mycophenolate mofetil and the so-called biological drugs and combinations (apart from the exceptions mentioned above) are still seeking their place in the management of vasculitis.

TRAVELOGUE: CONCLUSION AND SUMMARY

Conclusion

General practitioners have an important task in screening rare, but severe and often life-threatening vasculitis patients from their large patient flow. Careful patient history and physical examination are the cornerstones of success. Targeted basic laboratory tests and imaging studies help to differentiate pseudovasculitis and secondary from primary vasculitis. Patients who are suspected to have clinically significant vasculitis should then be urgently referred to specialized centres for invasive histological and radiological diagnosis confirmation, initiation of immunosuppressive treatment, and follow-up.

Summary

Vasculitis is characterized by vessel-wall injury caused by an immunoinflammatory process. Vessel-wall injury may lead to: (a) vascular aneurysm, dissection and bleeding; (b) stenosis, occlusion, thrombosis, embolism and ischemia; or (c) tissue injury-induced granulomatous or non-granulomatous inflammation, and oedema caused by an increased capillary hydrostatic pressure. Vasculitis is clinically important when the patient has general inflammatory and multifocal organ symptoms, which progress in episodes and can be explained by these vascular lesions. The clinical manifestations depend on the size, site and type of the blood vessels involved in

different organs and tissues. This forms the basis of the current classification of primary vasculitides. It is important to recognize secondary vasculitides, as their treatment is mainly based on the elimination of the triggering factor. In primary vasculitides, immunosuppression alone is the basis of treatment in almost all cases. Management of pseudovasculitis is dependent on the aetiology. In primary care, basic evaluation should be done: patient history, physical examination, basic laboratory tests and other non-invasive tests to verify suspected surrogate findings. After this, patients with "unstable vasculitic plaque" (substrate for thrombus formation) and potentially multiple vital organ-threatening disease should be urgently referred to a specialized centre, where the necessary histological and radiological diagnostic work-up is carried out and appropriate (mostly, immunosuppressive) treatment is initiated.

REFERENCES

1. Luqmani RA, Bacon PA, Moots RJ, Janssen BA, Pall A, Emery P, et al. Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. QJM 1994; 87: 671–8.

2. Exley AR, Bacon PA, Luqmani RA, Kitas GD, Gordon C, Savage CO, et al. Development and initial validation of the Vasculitis Damage Index for the standardized clinical assessment of damage in the systemic vasculitides. Arthritis Rheum 1997; 40: 371–80.

3. Langford CA. Management of systemic vasculitis. Best Practice Res Clin Rheumatol 2001; 15: 281–97.

4. Luqmani RA, Pathare S, Kwok-Fai TL. How to diagnose and treat secondary forms of vasculitis. Best Practice Res Clin Rheumatol 2005; 19: 321–36.

5. Pipitone N, Boiardi L, Salvarani C. Are steroids alone sufficient for the treatment of giant cell arteritis? Best Practice Res Clin Rheumatol 2005; 19: 277–92.

6. Valsakumar AK, Valappil UC, Jorapur V, Garg N, Nityanand S, Sinha N. Role of immunosuppressive therapy on clinical, immunological, and angiographic outcome in active Takayasu's arteritis. J Rheumatol 2003; 30: 1793–8.

7. Hoffman GS, Leavitt RY, Kerr GS, Rottem M, Sneller MC, Fauci AS. Treatment of glucocorticoid-resistant or relapsing Takayasu arteritis with methotrexate. Arthritis Rheum 1994; 37: 578–82.

8. Liang P, Hoffman GS. Advances in the medical and surgical treatment of Takayasu arteritis. Curr Opin Rheumatol 2005; 17: 18–24.

9. Jover JA, Hernandez-Garcia C, Morado IC, Vargas E, Banares A, Fernandez-Gutierrez 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.

10. Hoffman GS, Cid MC, Hellmann DB, Guillevin L, Stone JH, Schousboe J, 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.

11. Hoffman GS, Merkel PA, Brasington RD, Lenschow DJ, Liang P. Anti-tumor necrosis factor therapy in patients with difficult to treat Takayasu arteritis. Arthritis Rheum 2004; 50: 2296–304.

12. Andonopoulos AP, Meimaris N, Daoussis D, Bounas A, Giannopoulos G. Experience with infliximab (anti-TNF alpha monoclonal antibody) as monotherapy for giant cell arteritis. Ann Rheum Dis 2003; 62: 1116.

13. Jayne D. How to induce remission in primary systemic vasculitis. Best Practice Res Clin Rheumatol 2005; 19: 293–305.

14. Guillevin L, Lhote F, Gayraud M, Cohen P, Jarrousse B, Lortholary O, et al. Prognostic factors in polyarteritis nodosa and Churg–Straüss syndrome. A prospective study in 342 patients. Medicine (Baltimore) 1996; 75: 17–28.

15. Guillevin L, Mahr A, Callard P, Godmer P, Pagnoux C, Leray E, et al. French Vasculitis Study Group. Hepatitis B virus-associated polyarteritis nodosa: clinical characteristics, outcome, and impact of treatment in 115 patients. Medicine (Baltimore) 2005; 84: 313–22.

16. Burns JC, Glode MP. Kawasaki syndrome. Lancet 2004; 364: 533–44.

17. De Groot K, Rasmussen N, Bacon PA, Tervaert JW, Feighery C, Gregorini G, 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.

18. Langford CA, Talar-Williams C, Barron KS, Sneller MC. A staged approach to the treatment of Wegener's granulomatosis: induction of remission with glucocorticoids and daily cyclophosphamide switching to methotrexate for remission maintenance. Arthritis Rheum 1999; 42: 2666–73.

19. Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JW, Dadoniene J, et al. European Vasculitis Study Group. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic antibodies. N Engl J Med 2003; 349: 36–44.

20. Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. N Engl J Med 2005; 352: 351–61.

21. Booth A, Harper L, Hammad T, Bacon P, Griffith M, Levy J, et al. Prospective study of TNF alpha blockade with infliximab in anti-neutrophil cytoplasmic antibody-associated systemic vasculitis. J Am Soc Nephrol 2004; 15: 717–21.

22. Keogh KA, Wylam ME, Stone JH, Specks U. Induction of remission by B lymphocyte depletion in eleven patients with refractory antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2005; 52: 262–8.

23. Aries PM, Hellmich B, Voswinkel J, Both M, Nolle B, Holl-Ulrich K, et al. Lack of efficacy of rituximab in Wegener's granulomatosis with refractory granulomatous manifestations. Ann Rheum Dis 2006; 65: 853–8.

24. Danieli MG, Cappelli M, Malcangi G, Logullo F, Salvi A, Danieli G. Long term effectiveness of intravenous immunoglobulin in Churg–Straüss syndrome. Ann Rheum Dis 2004; 63: 1649–54.

25. Scheinfeld NS, Jones EL, Silvenberg N. Henoch-Schönlein purpura. E-medicine. http://www.emedicine.com/ped/topic 3020.htm.

26. Faedda R, Pirisi M, Satta A, Bosincu L, Bartoli E. Regression of Henoch-Schönlein disease with intensive immunosuppressive treatment. Clin Pharmacol Ther 1996; 60: 576–81.

27. Cacoub P, Saadoun D, Limal N, Sene D, Lidove O, Piette JC. PEGylated interferon alfa-2b and ribavirin treatment in patients with hepatitis C virus-related systemic vasculitis. Arthritis Rheum 2005; 52: 911–5.

28. Nesher G, Berkun Y, Mates M, Baras M, Rubinow A, Sonnenblick M. Low-dose aspirin and prevention of cranial ischemic complications in giant cell arteritis. 2004; 50: 1332–7.