Int. Adv. Otol. 2012; 8:(1) 130-136

CASE REPORT

Otological Granulomatosis with Polyangiitis (Wegener's Granulomatosis): Two Case Reports and an Update

James E Mitchell, David K Selvadurai

St George's Hospital, London, UK SW17 0RE (JEM, DKS)

Wegener's Granulomatosis (WG), more recently known as 'granulomatosis with polyangiitis', is a rare systemic disease of unknown aetiology, characterized by necrotizing granulomatous vasculitis affecting the upper and lower airways and kidneys. Otological involvement is more common than previously thought. Sensorineural hearing loss is generally regarded as irreversible in WG. However, up to 18% of patients' hearing may improve after treatment. We describe two cases of WG presenting with otological symptoms. One patient presented with acute suppurative otitis media and sensorineural hearing loss which completely recovered after treatment, which has not previously been reported. The second patient presented with mastoiditis. The otological characteristics, investigation and management of WG are discussed.

Submitted : 05 April 2011 *Accepted : 11 August 2011*

Introduction

Wegener's Granulomatosis is a rare condition which frequently affects the ear. We present two differing cases of patients presenting with otological Wegener's. The otological characteristics, investigation and management of this condition are discussed.

Case 1

Over a period of two months, an 18-year-old woman attended the otolaryngology outpatient department with a painful discharging left ear. An aural swab isolated diptherioids and proteus sp. and the patient was treated with appropriate topical antibiotic / steroid drops. During this period her contralateral ear became symptomatic. Her otorrhoea settled but the otalgia persisted. She also complained of increasing hearing loss and left sided tinnitus, but no vertigo.

She subsequently developed headaches and fevers and was admitted for intravenous antibiotics. A diagnosis of acute otitis media was made and ventilation tube insertion was performed. Pure tone audiometry demonstrated a profound sensorineural hearing loss in her left ear with a pure tone average (PTA) of 120 dB and a mixed hearing loss in her right ear (PTA 85dB) (Figure 1). Her tympanic membranes were thickened but no pus or effusion was evident after myringotomies. Blood c-ANCA PR3 screen was positive (35.7U/ml) and ESR was 30 mm/hr.

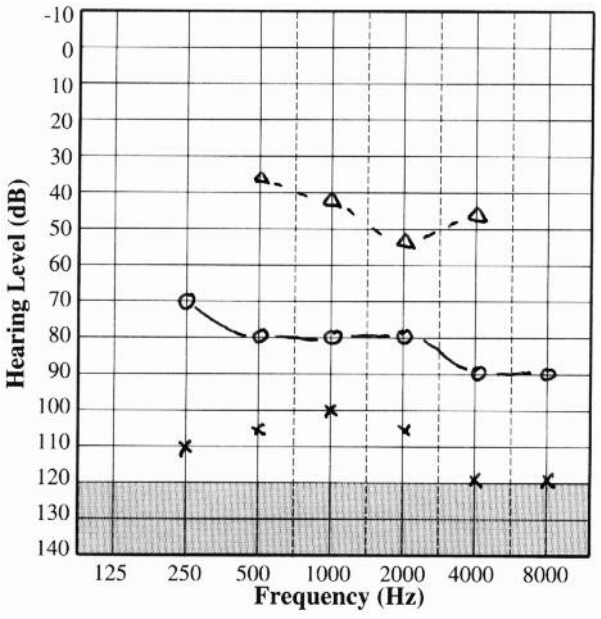

Figure 1. Initial Pure Tone Audiogram (case 1).

Corresponding address:
James E Mitchell
ENT Department St George's Hospital
London, SW17 0RE
Phone: +447841 921574, Fax: +44208 725 3306
E-mail: jamesmitchell@btopenworld.com

She was commenced on high dose oral steroids (Methyprednisolone 500mg once daily for three days followed by Prednisolone 1mg/kg once daily). Her symptoms of headaches, fever and otalgia quickly settled.

A CT scan demonstrated complete opacification of both mastoid and middle ear cavities. Some mild mucosal thickening was also noted in the para-nasal sinuses. Urine microscopy and renal ultrasound scan were normal.

Although she had no specific respiratory symptoms, a chest radiograph demonstrated a possible cavitating lesion in her right lower lobe, confirmed on CT scanning. Bronchoscopy however, failed to show any lesion. Washings showed no evidence of acid fast bacilli or other infection. Cytology demonstrated macrophages, lymphocytes and occasional benign bronchial epithelial cells with no siderophages or granulomas.

Her repeat pure tone audiograms demonstrated a rapid improvement in hearing in the right ear three days after commencement of steroids with a PTA of 35 dB (Figure 2). She was commenced on cyclophosphamide 2mg/kg daily and co-trimoxazole 960 mg three times daily, for a period of three months, to induce remission.

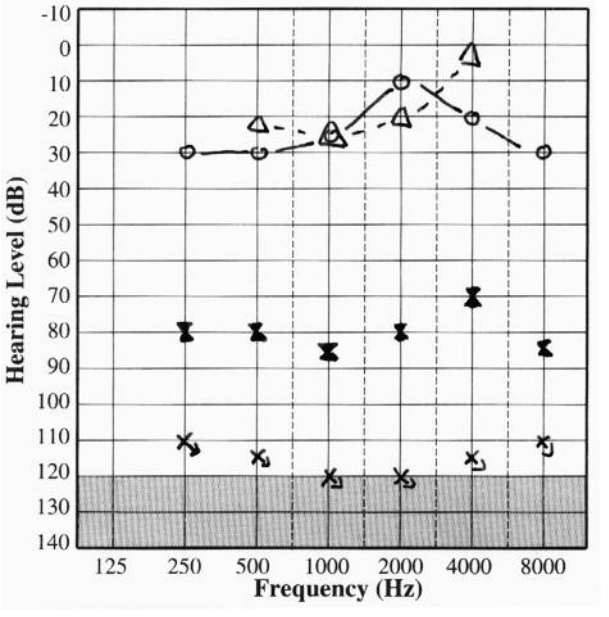

Figure 2. Final Pure Tone Audiogram (case 1)

She underwent regular outpatient follow-up with respiratory and otolaryngology services. After three months her co-trimoxazole and cyclophosphamide therapy was discontinued and she was commenced on Azothioprine 100mg daily. Her oral steroid dose was slowly reduced over a period of 24 months and eventually discontinued. Subsequent c-ANCAPR3 and ESR levels normalized. Her hearing thresholds normalized in her right ear completely, but she remained profoundly deaf in her left ear.

Case 2

A 59-year-old lady was admitted after four weeks of failed community treatment of a left chronic secretory otitis media. Her left tympanic membrane was inflamed with protruding granulation tissue. Her symptoms failed to settle on 48 hours of intravenous antibiotics. A CT scan demonstrated left mastoiditis. She underwent a left cortical mastoidectomy later that evening. Granulation tissue was seen filling the mastoid and prolapsing through a tympanic membrane perforation.

Over the next few days she remained pyrexial. She had persistently raised white cell and platelet counts and an ESR of 109. Pure tone audiograms demonstrated a left sided SNHL with a PTA of 90dB and a right mixed hearing loss with a PTA of 60dB (Figure 3).

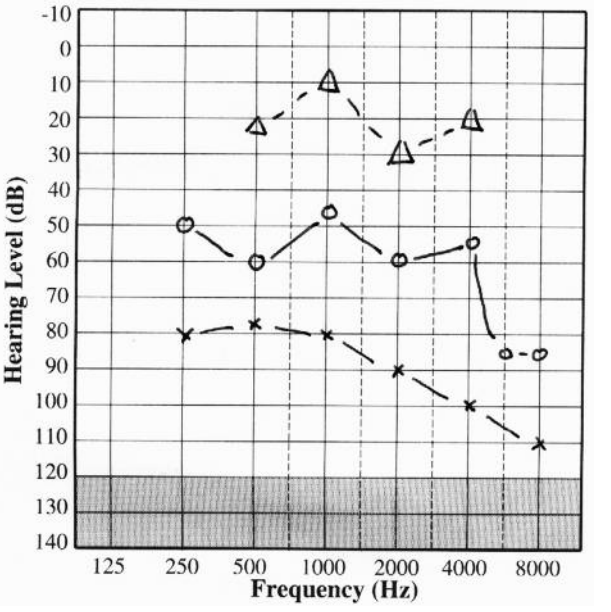

Figure 3. Initial Pure Tone Audiogram (case 2)

One week later she underwent a right myringotomy and exploration of left mastoidectomy. Turbid fluid was found in the left middle ear and a grommet placed. No collection was found in the left mastoid cavity.

A Chest radiograph demonstrated a left upper zone abnormality and a pleural effusion. Subsequently her c-ANCA was found to be positive with PR3 antibodies elevated at 14.3U/ml. A bronchoscopy was undertaken and a fine needle aspirate of the lung shadow was performed. Neither provided any diagnostic value. Renal ultrasound scan and urine analysis confirmed no renal involvement.

She was commenced on high dose oral steroids and Cyclophosphamide and co-trimoxazole. After one week she made a good recovery and showed improvement in her inflammatory markers. This treatment was continued for three months and her inflammatory markers and chest radiograph normalized. Her pure tone audiometry at this point shows normal hearing in the right ear and a moderate SNHL in the left ear with a PTA of 50 dB (Figure 4).

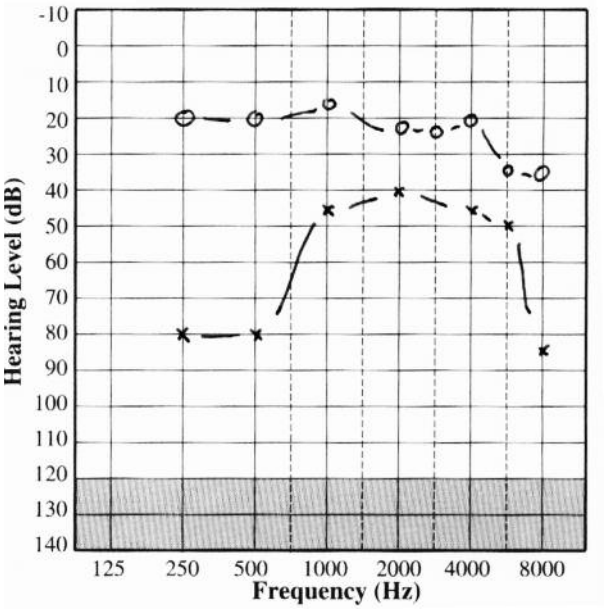

Figure 4. Final Pure Tone Audiogram (case 2)

Discussion

Wegener's granulomatosis (WG), more recently described as 'granulomatosis with polyangiitis', is a rare disease whose aetiology remains unclear.[1,2] The incidence and prevalence of WG is estimated at [8.4] per million and 64.8 per million respectively.[3] The typical age at diagnosis is 35-55 years. WG is more common in men (1.5:1 gender ratio).4 Although known to affect all ethnic groups, it has a strong tendency to affect Caucasians (98% of all patients).[2] Case two was of Asian ethnicity.

The aetiology is unknown, although environmental silica has been implicated.[5] Certain drugs are associated with vasculitis e.g. propylthiouracil.[6] Infectious agents are thought to initiate vasculitis and nasal carriage of Staphylococcus aureus is well documented in WG.[7,8]

In the classic form of WG, three regions are involved; the lung, kidney and head and neck. Some patients develop a limited form of WG where disease is limited to one or two regions only. Pulmonary involvement occurs in up to 85% of all WG patients. Although only 20% have renal involvement at time of diagnosis, glomerulonephritis eventually develops in up to 80% of WG patients. Skin and ocular manifestations are also very common during the course of the disease.[9]

ENT involvement is the presenting symptom in 63% of WG patients.[10] In a study of 155 patients, all examined by an ENT surgeon; 93% had ENT manifestations at the time of diagnosis and 99% did during the course of the disease.[11]

Otological features in WG include; otitis media, sensorineural hearing loss (SNHL), vertigo and facial nerve palsy.[212] A reported 19-61% of patients with WG have otologic findings, although presentation of WG with otological symptoms alone is uncommon.[13] One case report exists of WG limited only to the ear.[14] Unilateral or bilateral serous otitis media remain the commonest otological finding in WG. Acute mastoiditis as a presentation, as in our patient, is rare with one reported case (with a fatal outcome).[15] Inflammation and irritation from nasal secretions or granuloma formation within the middle ear, eustachian tube / nasopharynx is believed to be the cause of the serous otitis media seen in WG and resultant conductive hearing loss.[16,17] Some patients also suffer

with purulent otitis media, some of which will be due to granulomatous involvement of the middle ear or mastoid.[16] Facial nerve and other cranial nerve involvement are rare, but reported, and will usually improve with treatment.[16,17]

The reported prevalence of any hearing loss in WG ranges from 19-61%. Sensorineural hearing loss in WG varies from 2.8%[18] to 47%.[19] Hearing loss can be an early indicator of disease and will be the presenting symptom in up to 50%.[10,19] SNHL is significant because cranial nerve involvement may suggest severe disease requiring more aggressive treatment.[18] SNHL is generally regarded as being irreversible in WG, thus adding to the patient's morbidity.[20] However, one cohort reported 18% of patients' SNHL improving after treatment (with 59% remaining stable and 24% becoming worse).[19]

WG related audiometric tests are typically flat and occasionally with additional high tone loss which can make it difficult to distinguish from age or noise related loss. SNHL can progress from days to weeks. The pathogenesis of this is unclear, but might be due to inflammatory toxins entering through the round window from middle ear disease and / or from vasculitis of the vasa nervorum and cochlear vessels.[21] Many of these patients with SNHL will develop tinnitus, but vertigo is rare. Unusually in our patient, one ear made a complete recovery from SNHL. This appears not to have been reported previously.

WG is associated with circulating antineutrophil cytoplasm antibodies (c-ANCA) whose target antigen is proteinase 3 (PR3) located in the azurophilic granules of neutrophils and monocytes. The prevailing theory is that c-ANCA-activated cytokine-primed neutrophils induce microvascular damage and a rapid escalation of inflammation with recruitment of mononuclear cells.[22] Immunofluorescence c-ANCA is positive in 87% of patients with active full-blown disease and in 90% of those with limited disease.18 For patients in remission, the sensitivity falls to approximately 30%. C-ANCA is highly specific for WG and can be used for initial diagnosis as well as a marker of disease activity.[23]

A positive p-ANCA (whose target antigen is primarily myeloperoxidase) occurs in 13% of WG patients.[18] P-ANCA positivity may also occur in other diseases such as Churg-Strauss vasculitis, Sjogren's syndrome, Crohn's disease, lupus, temporal arteritis and polymyalgia rheumatica.[24] False positive c-ANCAs are reported to occur in <5% of cases of WG.[25] Very few WG patients are ANCA negative.[26] Other characteristic laboratory findings include an elevated erythrocyte sedimentation rate, which is seen in 94-100%[27] of WG cases. Anaemia may be present in 50-70% of patients.[27]

Making a diagnosis of WG can be challenging. Diagnostic criteria exist from The American College of Rheumatology (which has a diagnostic sensitivity of 88% and specificity of 92%) and The Chapel Hill Consensus Conference criteria (which requires granulomatous inflammation of the respiratory tract and vasculitis of small to medium size vessels).[28,29] It is important to distinguish WG from other diseases, especially those which worsen with immunosuppressants. A biopsy might not be required for confirmation if the classic triad of upper airway, pulmonary and renal disease is present and c-ANCA-PR3 is positive. However, many cases will need biopsy to help make the diagnosis.[30]

In the fully developed form, the microscopic appearances of WG in the upper aerodigestive tract are a triad of necrosis, granulomatous inflammation and true vasculitis. Histologic changes may be patchy, and samples may not provide the diagnosis. Large samples increase the yield. Biopsies of ENT samples may only be positive in 20% of cases. The highest yield (91%) comes from open or thoracoscopic biopsy of pulmonary parenchymal lesions.[31] Since similar histologic features can be seen with infection, it is vital that infection is ruled out with special stains and cultures.

The current treatment of WG depends on the disease severity and organ involvement.[32] Current treatment standards use prednisolone and induction with short term daily cyclophosphamide[32] followed by substitution with less toxic agents e.g. methotrexate[33] or azathioprine.[34] Limited disease may respond to

single agents such as corticosteroids or methotrexate.[35] Untreated, mortality is 82% at 1year. 30 Treatment is continued for 3-12 months following remission and then the patient is treated with medication for maintenance of remission for at least [18] months. Trimethoprim-Sulphamethoxazole has been shown to reduce the rate of recurrence of nasal and upper airway lesions, but not that of major organ disease.[236] It is used when patients are induced with steroids and cytotoxics to prevent Pneumocystis jiroveci pneumonia. Other drug and treatment regimes have also been investigated including; Rituximab, intravenous immunoglobulin, Mycophenolate mofetil, 15-deoxyspergualin and inhibitors to tumour necrosis factor alpha.[30, 37-40]

The key to care of these patients is an interdisciplinary approach with regular surveillance. This affords the patient better identification of organ involvement and reduces morbidity, therapy complications and improves prognosis.[11] Awareness of WG as a potential diagnosis, improved therapies and the multidisciplinary approach may be responsible for the reduction in mortality and morbidity seen over recent decades.[3,41] Health related quality of life however, remains significantly reduced in WG patients even with limited disease and when in remission.[42]

Conclusion

Wegener's Granulomatosis is a rare condition, but otological involvement is common. All WG patients should have ENT surgeon involvement and screening audiometry. Those with hearing loss should have follow-up audiometric assessment. Conductive hearing loss will often improve after treatment, sensorineural loss is less likely to improve. A multi-disciplinary approach is essential in the assessment and treatment of these patients, and improves patient outcomes.

References

1. Falk RJ, Gross WL, Guillevin L, Hoffman G, Jayne DRW, Jennette JC et al. Granulomatosis with polyangiitis (Wegener's): An alternative name for Wegener's granulomatosis Ann Rheum Dis 2011; 70:704

2.Cotch MF, Hoffman GS, Yerg DE, Kaufman GI, Targonski P, Kaslow RA. The epidemiology of Wegener's granulomatosis. Estimates of the five-year period prevalence, annual mortality, and geographic disease distribution from population-based data sources. Arthritis Rheum 1996; 39:87-92

3. Watts RA, Al-Taiar A, Scott DG & Macgregor AJ. Prevalence and incidence of Wegener's granulomatosis in the UK general practice research database. Arthritis Rheum 2009; 61:1412-1416

4. Watts RA, Lane SE, Scott DG, Koldingsnes W, Nossent H, Gonzalez-Gay MA et al. Epidemiology of vasculitis in Europe. Ann Rheum Dis 2001; 60:1156-1157

5. Hogan SL, Satterly KK, Dooley MA, Nackman PH, Jennette JC, Falk RJ. Silica exposure in anti-neutrophil cytoplasmic autoantibody - associated glome-rulonephritis and lupus nephritis. J Am Soc Nephrol 2001; 12:134-142

6. Harper L, Cockwell P, Savage COS. Case of propylthiouracil-induced ANCA-associated small vessel vasculitis. Nephrol Dial Transplant 1998; 13:455-458

7. Zycinska K, Wardyn KA, Zielonka TM, Demkow U, Traburzynski MS. Chronic crusting, nasal carriage of Staphylococcus aureus and relapse rate in Wegener's granulomatosis. J Physiol Pharm 2008: 59(s6):825-831

8. Boudewyns A, Verbelen J, Koekelkoren E, Van Offel J, Van de Heyning P. Wegener's granulomatosis triggered by infection? Acta Otorhinolaryngol Belg 2001; 55:57-63

9. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, Rottem M, Fauci AS. Wegener's granulomatosis: an analysis of 158 patients. Ann Intern Med 1992; 116:488-498

10. Srouji IA, Andrews P, Edwards C, Lund VJ. Patterns of presentation and diagnosis of patients with Wegener's granulomatosis. J Laryngol Otol 2007; 121:653-658

11. Reinhold-Keller E, Beuge N, Latza U, De Groot K, Rudert H, Nolle B et al. An interdisciplinary approach to the care of patients with Wegener's granulomatosis:

long term outcome in 155 patients. Arthritis Rheum 2000; 43:1021-1032

12. Takagi D, Nakamaru Y, Magachi S, Faruta Y, Fukuda S. Otologic manifestations of Wegener's granulomatosis. Laryngoscope 2002; 112:1684-1690

13. Murty GE. Wegener's granulomatosis: Otorhinolaryngological manifestations. Clin Otolaryngol 1990; 15:385-393

14. Ito Y, Shinogo J, Yuta A, Okada E, Taki M, Matsukage H. A case report of Wegener's granulomatosis limited to the ear. Auris Nasus Larynx 1991; 18:281-289

15. Preuss SF, Stenner M, Beutner D, Laudes M, Klussmann JP. Fatal course of Wegener's granulomatosis with bilateral otomastoiditis and bilateral facial palsy. Otolaryngol Head & Neck Surg 2008; 138:799-800

16. McCaffrey TV, McDonald TJ, Facer GW, DeRemee RA. Otologic manifestations of Wegener's granulomatosis. Otolaryngol Head Neck Surg 1980; 88:586-593

17. Kornblut AD, Wolff SM, Fauci AS. Ear disease in patients with Wegener's granulomatosis. Laryngoscope 1982; 92:713-717

18. Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Limited versus severe Wegener's granulomatosis: baseline patient data on patients in the Wegener's granulomatosis etanercept trial. Arthritis Rheum 2003; 48:2299-2309

19. Bakthavachalum S, Driver MS, Cox C, Spiegel JH, Grundfast KM, Merkel PA. Hearing loss in Wegener's granulomatosis. Otol & Neurotol 2004; 25:833-837

20. Dekker PJ. Wegener's granulomatosis: otological aspects. J Otolaryngol 1993; 22:364-367

21. Stone JH, Francis HW. Immune-mediated inner ear disease. Curr Opin Rheumatol 2000; 12:32-40

22. Harper L, Savage COS. Pathogenesis of ANCA-associated systemic vasculitis. J Pathol 2000; 190:349-359

23. Thornton MA, O'Sullivan TJ. Otological Wegener's granulomatosis: a diagnostic dilemma. Clin Otolaryngol 2000; 25:433-434

24. Ferlito A, Devaney KO, Anniko M, Arnold W, Rinaldo A. Otological Wegener's granulomatosis at the time of initial presentation: a potential diagnostic dilemma. Acta Otolaryngol 2003; 123:675-677

25. Jeanette JC , Falk RJ. Antineutrophil cytoplasmic autoantibodies in inflammatory bowel disease. Am J Clin Pathol 1993; 99:221-223

26. Finkielman JD, Lee AS, Hummel AM, Viss MA, Jacob GL, Homburger HA et al. ANCA are detectable in nearly all patients with active severe Wegener's Granulomatosis. Am J Med 2007; 120:643.e9-14

27. Fauci AS, Haynes BF, Katz P, Wolff SM. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. Ann Intern Med 1983; 98:76-85

28. Leavitt RY, Fauci AS, Bloch DA, Michel BA, Hunder GG, Arend WP et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthitis Rheum 1990; 33:1101-1107

29. Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL et al. Nomenclature of systemic vasculitides. Proposal of an International Consensus Conference. Arthritis Rheum 1994; 37: 187–92

30. Mubashir E, Ahmed MM, Hayat S, Latif S, Heldmann M. Berney SM. Wegener's granulomatosis: A case report and update. Southern Med J 2006; 99:977-988

31. Langford CA. Update on Wegener's granulomatosis. Cleve Clin J Med 2005; 72:689-690, 693-697

32. Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis 2009; 68:310-317

33. Langford CA, Talar-Williams C, Barron KS, Sneller MC. Use of cyclophosphamide-induction methotrexate-maintenance regimen for the treatment of Wegener's granulomatosis: extended follow-up and rate of relapse. Am J Med 2003; 114:463-469

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

35. Frankel SK, Cosgrove GP, Fischer A. Update in the diagnosis and management of pulmonary vasculitis. Chest 2006; 129:452-65

36. Stegeman CA, Tervaert JW, de Jong PE, Kallenberg CG. Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. Dutch Co-Trimoxazole Wegener Study Group. N Engl J Med 1996; 335:16-20

37. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010; 363:221-232

38. Martinez V, Cohen P, Pagnoux C, et al. 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; 58:308-371

39. Koukoulaki M, Jayne DR. Mycophenolate mofetil in anti-neutrophil cytoplasm antibodies-associated systemic vasculitis. Nephron Clin Pract 2006; 102:c100-7

40. Schmitt WH, Birck R, Heinzel PA, Gobel U, Choi M, Warnatz K et al. Prolonged treatment of refractory Wegener's granulomatosis with 15-deoxyspergualin: an open study in seven patients. Nephrol Dial Transplant 2005; 20:1083-1092

41. Holle JU, Gross WL, Latzu U, Nolle B, Ambrosch P, Heller M et al. Improved ourcome in 445 patients with Wegener's granulomatosis in a German vasculitis center over four decades. Arthritis Rheum 2011; 63:257-266

42. Faurschou M, Sigaard L, Bjorner JB, Baslund B. Impaired health-related quality of life in patients treated for Wegener's granulomatosis. J Rheumatol 2010; 37:2081-2085