Kidney transplantation should be considered as first option in remission of the disease and remission maintenance strategies. MPA consists of remission induction strategies in order to achieve still the gold standard of the diagnosis of MPA. The therapy of been proposed [5]. Histological confirmation of vasculitis remains pathogenesis of MPA. In addition, a pathogenic role for ANCAs has in association with a genetic predisposition are involved in the unknown. There is increasing evidence that environment factors due to pulmonary capillaritis [1,2]. The pathogenesis of MPA is

Lung manifestations consist of diffuse alveolar haemorrhage [3g] and hypertension. Lungs are usually also affected in MPA. The kidneys and lungs are the most typical organs involved in MPA. Notably, MPA is the major cause of pulmo-renal syndrome. MPA has a poor prognosis if not treated but the use of aggressive immunosuppressive treatment has improved the prognosis and the patient’s survival. Rituximab could be considered as an alternative treatment for severe disease, for patients who do not respond adequately to the immunosuppressive treatment and for patients with relapses. However, the long-term safety of Rituximab in MPA is unknown and it should be elucidated by further studies. Interestingly, kidney transplantation is safe and effective and it has a good prognosis in MPA patients with ESRD.

**Keywords:** ANCAs; Microscopic polyangiitis; Treatment; Vasculitis

### Microscopic Polyangitiis: from Pathogenesis to Treatment

**Abstract**

Microscopic Polyangiitis (MPA) is a systemic pauci-immune necrotizing vasculitis of small-calibre vessels characterized by the absence of granulomas. MPA is an autoimmune disease but its aetiology remains obscure. MPA is associated with presence of antineutrophil cytoplasmatic autoantibodies (ANCAs) but not all patients with MPA have ANCAs. There is strong evidence that not all ANCAs are pathogenetic. It seems that specific epitopes determine ANCAs pathogenicity. Given that MPA is a systemic vasculitis, multiple organs could be affected resulting in a wide spectrum of signs and symptoms. The kidneys and lungs are the most typical organs involved in MPA. Notably, MPA is the major cause of pulmo-renal syndrome. MPA has a poor prognosis if not treated but the use of aggressive immunosuppressive treatment has improved the prognosis and the patient’s survival. Rituximab could be considered as an alternative treatment for severe disease, for patients who do not respond adequately to the immunosuppressive treatment and for patients with relapses. However, the long-term safety of Rituximab in MPA is unknown and it should be elucidated by further studies. Interestingly, kidney transplantation is safe and effective and it has a good prognosis in MPA patients with ESRD.

**Keywords:** ANCAs; Microscopic polyangiitis; Treatment; Vasculitis

### Introduction

The term vasculitides refers to a group of inflammatory disorders involving any size or type of vessel. Microscopic Polyangiitis (MPA) is a systemic pauci-immune vasculitis of glomerular capillaries leading to necrotizing glomerulonephritis [1]. Renal involvement is particularly frequent in small vessel systemic necrotizing vasculitis called anti-neutrophil cytoplasmatic autoantibody associated vasculitis (AAV), including MPA, granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis. Renal involvement in MPA is of particular importance because it is associated with poor prognosis and increased mortality [2]. In particular, the presence of renal impairment and dialysis dependence at diagnosis increases the risk of death in AAV patients [3,4].

The main clinical presentation in MPA is rapidly progressive glomerulonephritis (RPGN) characterized by rapid decrease of glomerular filtration rate (GFR), microscopic haematuria, erythrocyte cast presence of proteinuria (usually less than 3g) and hypertension. Lungs are usually also affected in MPA. Lung manifestations consist of diffuse alveolar haemorrhage due to pulmonary capillaritis [1,2]. The pathogenesis of MPA is unknown. There is increasing evidence that environment factors in association with a genetic predisposition are involved in the pathogenesis of MPA. In addition, a pathogenic role for ANCAs has been proposed [5]. Histological confirmation of vasculitis remains still the gold standard of the diagnosis of MPA. The therapy of MPA consists of remission induction strategies in order to achieve remission of the disease and remission maintenance strategies. Kidney transplantation should be considered as first option in AAV patients which are in remission more than one year [6].

### History

In 1866, Kaussmal and Maier were the first to describe completely a case report of a 27-year old man with systemic vasculitis. The term polyarteritis nodosa (PN) was introduced to describe all the patients with non infectious arteritis [1]. In 1923, a new distinct entity from PN was described the so-called “microscopic form of periarteritis nodosa” characterized both by the presence of glomerulonephritis and non granulomatous inflammation [7]. Later, a stretch correlation of “microscopic form of periarteritis nodosa” with Wegener’s granulomatosis and Churg-Strauss syndrome now called granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis was described respectively [8]. In 1985, the term microscopic polyarteritis was replaced by the term microscopic polyangiitis [9]. After three years Jennette and Falk reported an association of the disease with ANCAs [10]. In 1994 the Chapel Hill Consensus Conference (CHCC) introduced the term microscopic polyangiitis describing a small vessel vasculitis characterized by rapid progressive glomerulonephritis and pulmonary capillaritis with the absence of immune complex deposition on immunofluorescence [2]. Finally, according to 2012 revision of CHCC classification, MPA was reported as a pauci -immune small-vessel vasculitis with absence of granulomas or eosinophilia associated with myeloperoxidase (MPO- ANCA)[1,12].

### Epidemiology

An increased incidence has been reported especially in
Microscopic Polyangiitis: from Pathogenesis to Treatment

Dousdampanis P, Assimakopoulos SF, Trigka K (2017) Microscopic Polyangiitis: from Pathogenesis to Treatment. Urol Nephrol Open Access J. In [30]. Peripheral neuropathy (mononeuritis-symmetrical polyneuropathy) is the predominant manifestation while involvement of the central nervous system has also been reported [31]. Ear nose and throat manifestations are less frequent in MPA patients [31].

Diagnosis

At present, there is no specific diagnostic tool for MPA. Diagnosis should be based on clinical symptoms and signs from various systems affected and on pathological feature. Specific markers of inflammation including leukocytosis, increased sedimentation velocity, increased CRP and normocytic anaemia are indicative but not diagnostic for MPA disease. The absence of ANCAs does not exclude the diagnosis. Pathological feature of pauci-immune necrotizing small-vessel vasculitis in biopsy confirms the diagnosis of MPA. The absence of granulomatous inflammation differentiates MPA from GPA [32].

Prognosis

The prognosis of MPA is poor without treatment (annual mortality rate above 90%). Interestingly, the introduction of aggressive immunosuppressive drugs has substantially improved the prognosis [2]. More specifically, the cumulative survival of MPA patients with renal involvement at 1 and 5 years was 82% and 76% respectively [5]. ESRD observed in 28% of MPA patients. Risk factors for ESRD were serum creatinine at the time of the diagnosis, African American race and severity of histological lesions at biopsy [5]. The mortality in ESRD patients due to MPA was around 50% the prognosis was worse in patients with pulmonary syndrome [33,34]. Death occurring during the first year of MPA immunosuppressive treatment was related primarily to insufficient treatment response, several infections, cardiovascular disease and malignancy [4]. Disease relapse occurred in 35% of MPA patients [5].

Treatment

Induction treatment consists of immunosuppressant’s including cyclophosphamide (2mg/kg/day for 3-6 months) plus corticosteroids (1mg/kg/day) with tapering. In more severe cases can precede the use of methylprednisolone iv (500mg or 1 gr 3 times). Intravenous pulse cyclophosphamide (15mg/kg) is also effective compared to oral treatment with lesser side effects. In more severe cases, with renal failure and lung involvement plasma exchange is indicated (seven exchanges over 2 weeks). Use of plasma infusion is limited to patients with relapse or to those resistant to immunosuppression treatment [7]. The long term effect of plasmapheresis on patients’ outcome is unknown. Whether duration of plasma exchange therapy should be tailored to ANCA titers has not been yet studied.
Once remission (absence of clinical manifestations of GN) has been obtained, maintenance therapy with Azathioprine (AZA) (2mg/kg/day) for 12 months should be added. Mycophenolate mofetil (MMF) is an alternative but it is less effective than AZA. Rituximab (anti-CD20) (375 mg/m² once weekly for 4 weeks) plus corticosteroids per os even without maintenance treatment has been proposed as an alternative to immunosuppressants (cyclophosphamide switched to AZA as maintenance therapy) for induction of remission in severe cases with renal involvement and in patients which do not respond to immunosuppression. Moreover, Rituximab could be considered as another effective option for the relapses. However, the long-term toxicity of Rituximab should be elucidated by further studies.

Renal transplantation

Despite the major advances in the treatment of MPA, a large number of patients with MPA develop end stage renal disease (ESRD) [35]. AAV patients with ESRD on dialysis have a worse prognosis compared to those without dialysis independent renal function [36]. However, the overall mortality of AAV patients on dialysis is similar to those non-diabetic patients on dialysis [37-39]. Renal transplantation (RTx) is the first choice of treatment in these patients. According to Kidney Disease: Improving Global Outcomes (KDIGO) Guidelines for Glomerulonephritis [6], RTx is another therapeutic option in AAV patients with more than one year of disease remission [6]. Of note, the definition of remission is not widely accepted by all but usually it requires the absence of systemic clinical symptoms. In addition, ANCA positivity at the time of RTx should not be considered as a contraindication [35]. The risk of relapse is present but usually it decreases after RTx due to the more efficient anti-rejection therapy and the use of the immunosuppressant’s [40,41]. The treatment for disease relapses after transplantation in AAV patients does not differ from that of non kidney transplanted AAV patients. The increase dose of corticosteroids to plasma exchange therapy based on the severity of the disease [41,42]. Notably the use of cyclophosphamide remains also the gold standard and it has been successfully used in disease relapses after RTx. Rituximab could be considered as an alternative option to treat relapses after kidney transplantation [43,44].

Conclusion

1. Microscopic polyangiitis is a systemic idiopathic autoimmune disease involving small-calibre blood vessels.
2. ANCAs under certain circumstances are pathogenic.
3. Multiple organs are affected but predominantly kidneys and lungs are involved. Kidney involvement is characterized by rapidly progressive glomerulonephritis whereas diffuse alveolar haemorrhage due to capillaritis is the main pulmonary manifestation.
4. The diagnosis is based on clinical symptoms and ANCA detection but tissue biopsy is the gold standard.
5. Older age, females, serum creatinine at diagnosis, chronic lesions and crescents at renal biopsy and response to therapy and flares are predictive factors for kidney function.
6. The choice of therapy should be based on disease severity. Treatment strategies include cyclophosphamide with corticosteroids as therapy induction and Azathioprine as a remission maintenance therapy. However, Rituximab should be considered as an alternative therapy for patients who do not respond to immunosuppressant’s and for disease relapses.
7. Kidney transplantation is safe and effective and has a good prognosis in AAV patients with ESRD.

References

1. Chung SA, Seo P (2010) Microscopic polyangiitis. Rheum Dis Clin North Am 36(3): 545-558.
2. Greco A, De Virgilio A, Rizzo M, Gallo A, Magliulo G, et al. (2015) Microscopic polyangiitis: Advances in diagnostic and therapeutic approaches. Autoimmun Rev 14: 837-844.
3. Mukhtyar C, Flossmann O, Hellmich B, Bacon P, Cid M, et al. (2008) Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism systemic vasculitis task force. Ann Rheum Dis 67(7): 1004-1010.
4. Flossmann O, Berden A, de Groot K, Hagen C, Harper L, et al. (2011) Long-term patient survival in ANCA-associated vasculitis. Ann Rheum Dis 70(3): 488-494.
5. Kallenberg CG (2014) The diagnosis and classification of microscopic polyangiitis. Autoimmun Rev 14: 90-93.
6. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Working Group (2012) KDIGO clinical practice guideline for glomerulonephritis. Kidney Int Suppl 2: 139-274.
7. Wohllibl F (1923) Über die nur mikroskopisch erkennbare Form der Periarteritis nodosa. Virchows Arch Pathol Physiol 246: 36.
8. Goldman G, Churg J (1954) Wegener’s granulomatosis: pathology and review of the literature. AMA Arch Pathol 58(6): 533-553.
9. Savage CO, Winearls CG, Evans DJ, Rees AJ, Lockwood CM (1985) Microscopic polyarteritis: presentation, pathology and prognosis. Q J Med 56(220): 467-483.
10. Falk RJ, Jennette JC (1988) Anti-neutrophil cytoplasmic autoantibodies with specificity for myeloperoxidase in patients with systemic vasculitis and idiopathic necrotizing and crescentic glomerulonephritis. N Engl J Med 318(25): 1651-1657.
11. Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, et al. (1994) Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum 37(2): 187-192.
12. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, et al. (2013) 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 65(1): 1-11.
13. Mahr A, Guillemin L, Poissonnet M, Aymé S (2004) Prevalences of polyarteritis nodosa, microscopic polyangiitis, Wegener’s granulomatosis, and Churg-Strauss syndrome in a French urban multietnic population in 2000: a capture-recapture estimate. Arthritis Rheum 51(1): 92-99.
14. Koldingnes W, Nosent H (2000) Epidemiology of Wegener's granulomatosis in northern Norway. Arthritis Rheum 43(11): 2481-2487.

15. Mohammad AJ, Jacobsson LT, Mahr AD, Sturfelt G, Segelmark M (2007) Prevalence of Wegener's granulomatosis, microscopic polyangiitis, polyarteritis nodosa and Churg-Strauss syndrome within a defined population in southern Sweden. Rheumatology (Oxford) 46(8): 1329-1337.

16. Frankel SK, Jayne D (2010) The pulmonary vasculitides. Clin Chest Med 31(3): 519-536.

17. Guillemin L, Durand-Gasselin B, Celvallos R, Gagraud M, Lhoete F, et al. (1999) Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. Arthritis Rheum 42(3): 421-130.

18. Agard C, Mouthon L, Mahr A, Guillemin L (2003) Microscopic polyangiitis and polyarteritis nodosa: how and when do they start? Arthritis RHEUM 49(5): 709-715.

19. Hogan SL, Satterly KK, Dooley MA, Nachman PH, Jennette JC, et al. (2001) Silica exposure in anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis and lupus nephritis. J Am Soc Nephrol 12(1): 134-142.

20. Flossmann O, Berden A, de Groot K, Hagen C, Harper L, et al. (2011) Long-term patient survival in ANCA-associated vasculitis. Ann Rheum Dis 70(3): 488-494.

21. Little MA, Smyth CI, Yadav R, Ambrose L, Cook HT, et al. (2005) Antineutrophil cytoplasmic antibodies directed against myeloperoxidase augment leukocyte-microvascular interactions in vivo. Blood 106(8): 2050-2058.

22. Xiao H, Heeringa P, Hu P, Liu Z, Zhao M, et al. (2002) Antineutrophil cytoplasmic autoantibodies specific for myeloperoxidase cause glomerulonephritis and vasculitis in mice. J Clin Invest 110(7): 955-963.

23. Huugen D, Tervaert JW, Heeringa P (2004) Antineutrophil cytoplasmic autoantibodies and pathophysiology: new insights from animal models. Curr Opin Rheumatol 16(1): 4-8.

24. Schlieben DJ, Korbet SM, Kimura RE, Schwartz MM, Lewis EJ (2005) Pulmonary-renal syndrome in a newborn with placent al transmission of ANCA. Am J Kidney Dis 45(4): 758-761.

25. Land J, Rutgers A, Kallenberg CG (2014) Anti-neutrophil cytoplasmic autoantibody pathogenity revisited: pathogenic versus non-pathogenic anti-neutrophil cytoplasmic autoantibody. Nephrol Dial Transplant 29(4): 739-745.

26. Hedger N, Stevens J, Drey N, Walker S, Roderick P (2000) Incidence and outcome of pauci-immune rapidly progressive glomerulonephritis in Wessex, UK: a 10-year retrospective study. Nephrol Dial Transplant 15(10): 1593-1599.

27. Eisenberger U, Fakhouri F, Vanhille P, Beaufils H, Mahr A, et al. (2005) ANCA-negative pauci-immune renal vasculitis: histology and outcome. Nephrol Dial Transplant 20(7): 1392-1399.

28. Khan A, Lawson CA, Quinn MA, Isdale AH, Green MJ (2010) Successful Treatment of ANCA-Negative Wegener's Granulomatosis with Rituximab. J Rheumatol 2010: 846606.

29. Roth AJ, Ooi JD, Hess JJ, van Timmeren MM, Berg EA, et al. (2013) Epitope specificity determines pathogenicity and detectability in ANCA-associated vasculitis. J Clin Invest 123(4): 1773-1783.

30. Lyons PA, Rayner TE, Trivedi S, Holle JU, Watts RA, et al. (2012) Genetically distinct subsets within ANCA-associated vasculitis. N Engl J Med 367: 214-223.

31. Villiger PM, Guillevin L (2010) Microscopic polyangiitis: Clinical presentation. Autoimmun Rev 9(12): 812-819.

32. Watts R, Lane S, Handslik T, Hauser T, Hellrich B, et al. (2007) Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. Ann Rheum Dis 66(2): 222-227.

33. Booth AD, Almond MK, Burns A, Ellis P, Gaskin G, et al. (2003) Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. Am J Kidney Dis 41(4): 776-784.

34. Niles JL, Bottinger EP, Saurina GR, Kelly KJ, Pan G, et al. (1996) The syndrome of lung hemorrhage and nephritis is usually an ANCA-associated condition. Arch Intern Med 156(4): 446-445.

35. Hruskova Z, Geetha D, Tesar V (2015) Renal transplantation in anti-neutrophil cytoplasmic antibody-associated vasculitis. Nephrol Dial Transplant 30 Suppl 1: 1159-163.

36. de Joode AA, Sanders JS, Stegeman CA (2013) Renal survival in proteinase 3 and myeloperoxidase ANCA-associated systemic vasculitis. Clin J Am Soc Nephrol 8(10): 1709-1717.

37. Weidanz F, Day CJ, Hewins P, Savage C, Harper L (2007) Recurrences and infections during continuous immunosuppressive therapy after beginning dialysis in ANCA-associated vasculitis. Am J Kidney Dis 50(1): 36-46.

38. Tang W, Bose B, McDonald SP, Hawley CM, Badve SV, et al. (2013) The outcomes of patients with ESRD and ANCA-associated vasculitis in Australia and New Zealand. Clin J Am Soc Nephrol 8(5): 773-780.

39. Hruskova Z, Stel VS, Jayne D, Aasarad K, De Meester J, et al. (2015) Characteristics and Outcomes of Granulomatosis With Polyangiitis (Wegener) and Microscopic Polyangiitis Requiring Renal Replacement Therapy: Results From the European Renal Association-European Dialysis and Transplant Association Registry. Am J Kidney Dis 66(4): 613-620.

40. Allen A, Pusey C, Gaskin G (1998) Outcome of renal replacement therapy in antineutrophil cytoplasmic antibody-associated systemic vasculitis. J Am Soc Nephrol 9(7): 1258-1263.

41. Geetha D, Seo P (2007) Renal transplantation in the ANCA-associated vasculitides. Am J Transplant 7(12): 2657-2662.

42. Nachman PH, Segelmark M, Westman K, Hogan SL, Satterly KK, et al. (1999) Recurrent ANCA-associated small vessel vasculitis after transplantation: A pooled analysis. Kidney Int 55(4): 1544-1550.

43. Murakami C, Manoharan P, Carter-Monroe N, Geetha D (2013) Rituximab for remission induction in recurrent ANCA-associated glomerulonephritis post-kidney transplant. Transplant Int 26(12): 1225-1231.

44. Geetha D, Seo P, Specks U, Fervenza FC (2007) Successful induction of remission with rituximab for relapse of ANCA-associated vasculitis post-kidney transplant: report of two cases. Am J Transplant 7(12): 2821-2825.