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LETTER TO THE EDITOR

# The challenge of Wegener's granulomatosis after kidney transplantation

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End-stage renal disease caused by antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) is a rare event with five cases per million per year. Still there is growing recognition of the risk of relapse of the disease in kidney transplant recipients (KTR). While relapse of AAV is high in dialysis patients (up to 50%), it decreases after kidney transplantation (KTx; 8.6–22.2%) [1–3]. Yet, relapse may occur at any time after KTx and transplant involvement has been documented in at least 28 cases. Therapeutic guidelines for AAV after KTx do not exist and clinical management is discussed controversially. Prompted by two unusual cases of young male patients with smoldering AAV who recently underwent KTx at our hospital, we focus on the right point of time for transplantation, role of ANCAs, risk assessment, clinical presentation of flares and immunosuppression in relapse including treatment with rituximab.

Although it has never been formally studied, there is common belief that KTx in Wegener's granulomatosis (WG) is favourable when the patient is in stable remission. In KTx from deceased donors, the 'optimal' point of time is not foreseeable and thus cannot be planned. The question whether it is advisable to transplant a patient in a state of smoldering disease or to wait until he is in clear remission is not really answered in the literature. Anti-PR3–ANCAs (proteinase 3) are known as *markers of clinical activity* in WG and are seen in the generalized form in 70–80% of the patients [4]. Persistent or reappearing cytoplasmic-ANCA positivity in patients in remission was found to be significantly associated with relapse within the first year of disease [5]. Several mostly retrospective studies attempted to evaluate ANCA as *predictors of relapse*. Analysing these reports, 25–42% of the patients did not have a relapse despite elevated ANCA titres (Mukhtyar, 2008 no. 72). Thus, for WG ANCA titres alone do not seem a reliable tool for guiding preemptive treatment.

However, in some settings ANCA serologies may provide valuable information about disease activity. In one prospective study of 33 patients with disease relapse, only two patients showed no preceding rise in ANCA titre (both having persistently high ANCA levels, even during remission) [6]. Another study demonstrated, that PR3–ANCA levels >10 U/ml at 18 and 24 months were predictive of relapse within 5 years after treatment [7]. Despite these contradicting results, we do feel that ANCA titres still have diagnostic value in association with other criteria such as C-reactive protein levels and conscientious recognition of clinical symptoms. The sensitivity and specificity of anti-PR3 capture enzyme-linked immunosorbent assay (anti-PR3 classic ELISA, anti-PR3 capture ELISA) in diagnosing WG have been investigated recently as well as the correlation with the indirect immunofluorescence test (IIFT). The sensitivity of anti-PR3 classic ELISA and capture ELISA in diagnosing WG was 74% and 88%, respectively whereas specificity was identical (100%). The combination of IIFT with anti-PR3 capture ELISA increased sensitivity for WG patients up to 91.6% which is why it is recommended to apply both tests in parallel [8].

Estimating the risk of relapse in KTR of WG is important for choosing a treatment concept after KTx. According to a relatively huge prospective cohort analysis ($n = 350$) with 4 years of follow-up, the following factors were associated with relapse in 77% of the patients with AAV who had attained remission: (i) seropositivity for PR3–ANCA and (ii) disease of the lung or the upper respiratory tract. Relapses occurred in 73% of the patients with all three risk factors corresponding to a 3.7-fold increase in risk for relapse compared with patients with none of these factors ($P = 0.007$) [9].

The typical clinical presentation of WG is characterized by a rapid onset of glomerular haematuria, haemoptysis and nasal mucosal involvement. In contrast, symptoms of relapse after KTx vary widely with respect to onset, severity and organ involvement. Reports by Habits and Gera describe affection of the eyes as well as arthralgia and rash in some patients, while all of them had mild general symptoms with manifestation of the upper respiratory tract without KTx involvement [1,10]. Mild dyspnoea and microscopic haematuria seem to be the predominant symptoms of relapsing WG after KTx, but other individual symptoms such as arthralgia, bursitis and erythema can also predict disease activity.

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In fact, the choice of immunosuppressive therapy is a balancing act between risk and benefit, notably in WG with the predisposition to severe infection, relapse and rejection [11]. While in earlier studies KTR on cyclosporine (CsA) failed to show a lower relapse rate than KTR on azathioprine [12], new data support the impression, that modern immunosuppression including induction therapy, mycophenolate mofetil and tacrolimus (TAC) is favourable [13]. TAC-based regimen showed a relapse rate of 4% compared with 22% in the CsA-based regimen [1]. Further literature states that there was no difference in relapse rates when induction therapy (basiliximab, daclizumab, alemtuzumab versus no induction) was given prior to KTx [13,14].

For AAV recurrence cycles of prednisolone as well as cyclophosphamide (CYP) are known to be effective, and in some cases of pulmonary involvement and high titres of ANCA plasmapheresis therapy is added [10,15–17]. Still, these reports show a wide variety in respect of patient's criteria and treatment regimen and do not focus on KTR. Furthermore, several modern biological therapies with selective targets such as tumour necrosis factor inhibitors have failed to influence the course of AAV successfully. These facts underline the need for new therapeutic strategies including the pathophysiological understanding of AAV. ANCA are known to induce a necrotizing vasculitis and multiple other elements in the immune system: the exposure of a cryptic epitope is followed by an autoantibody response that produces ANCA. This antibody response may then generalize to the rest of the molecule by epitope spread. This hypothesis implies a role for T cells in the pathogenesis of the AAV [18]. In a cytometric assessment of patients with WG, T-cell activation persisted during remission of disease, while B-cell activation was related to active disease [19]. For the treatment of difficult-to-treat autoimmune diseases including AAV, there is upcoming evidence for the effectiveness of the monoclonal anti-CD-20 antibody rituximab [20,21]. The efficacy of rituximab on B-cell depletion is expressed on the one hand by a reduction of ANCA and on the other hand by interfering in the cellular immunity [22]. It has been effectively used off-label for patients with AAV refractory to CYP [23] and in KTR with relapsing WG [24]. Furthermore, rituximab seems to have a faster and more sustainable effect in patients with predominant vasculitis disease, as opposed to granulomatous manifestation. Currently, there is a randomized trial under way comparing rituximab and CYP in nontransplant patients with AAV [20].

To conclude, in KTR with AAV it is crucial to perform a multimodal risk assessment and to individualize immunosuppressive regimen as well as treatment of relapse carefully taking into account alternative therapeutic regimens such as e.g. rituximab.

## Conflicts of interest

None declared.

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## References

1. Gera M, Griffin MD, Specks U, Leung N, Stegall MD, Fervenza FC. Recurrence of ANCA-associated vasculitis following renal transplantation in the modern era of immunosupression. *Kidney Int* 2007; **71**: 1296.
2. Geetha D, Seo P. Renal transplantation in the ANCA-associated vasculitides. *Am J Transplant* 2007; **7**: 2657.
3. Elmedhem A, Adu D, Savage CO. Relapse rate and outcome of ANCA-associated small vessel vasculitis after transplantation. *Nephrol Dial Transplant* 2003; **18**: 1001.
4. Wiik A. Rational use of ANCA in the diagnosis of vasculitis. *Rheumatology (Oxford)* 2002; **41**: 481.
5. Stegeman CA. Anti-neutrophil cytoplasmic antibody (ANCA) levels directed against proteinase-3 and myeloperoxidase are helpful in predicting disease relapse in ANCA-associated small-vessel vasculitis. *Nephrol Dial Transplant* 2002; **17**: 2077.
6. Girard T, Mahr A, Noel LH, *et al.* Are antineutrophil cytoplasmic antibodies a marker predictive of relapse in Wegener's granulomatosis? A prospective study. *Rheumatology (Oxford)* 2001; **40**: 147.
7. Sanders JS, Huitma MG, Kallenberg CG, Stegeman CA. Prediction of relapses in PR3–ANCA-associated vasculitis by assessing responses of ANCA titres to treatment. *Rheumatology (Oxford)* 2006; **45**: 724.
8. Feng Z, Liu P, Li Z, Sui B. Clinical relevance of anti-PR3 capture ELISA in diagnosing Wegener's granulomatosis. *J Clin Lab Anal* 2008; **22**: 73.
9. Hogan SL, Falk RJ, Chin H, *et al.* Predictors of relapse and treatment resistance in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis. *Ann Intern Med* 2005; **143**: 621.
10. Haubitz M, Kliem V, Koch KM, *et al.* Renal transplantation for patients with autoimmune diseases: single-center experience with 42 patients. *Transplantation* 1997; **63**: 1251.
11. Schmitt WH, Haubitz M, Mistry N, Brunkhorst R, Erbsloh-Moller B, Gross WL. Renal transplantation in Wegener's granulomatosis. *Lancet* 1993; **342**: 860.

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12. Nachman PH, Segelmark M, Westman K, *et al.* Recurrent ANCA-associated small vessel vasculitis after transplantation: a pooled analysis. *Kidney Int* 1999; **56**: 1544.
13. Schmitt WH, van der Woude FJ. Organ transplantation in the vasculitides. *Curr Opin Rheumatol* 2003; **15**: 22.
14. Lee RW, D'Cruz DP. Novel therapies for anti-neutrophil cytoplasmic antibody-associated vasculitis. *Drugs* 2008; **68**: 747.
15. Moroni G, Torri A, Gallelli B, *et al.* The long-term prognosis of renal transplant in patients with systemic vasculitis. *Am J Transplant* 2007; **7**: 2133.
16. Nachman PH, Hogan SL, Jennette JC, Falk RJ. Treatment response and relapse in antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. *J Am Soc Nephrol* 1996; **7**: 33.
17. Nyberg G, Akesson P, Norden G, Wieslander J. Systemic vasculitis in a kidney transplant population. *Transplantation* 1997; **63**: 1273.
18. Seo P, Stone JH. The antineutrophil cytoplasmic antibody-associated vasculitides. *Am J Med* 2004; **117**: 39.
19. Popa ER, Stegeman CA, Bos NA, Kallenberg CG, Tervaert JW. Differential B- and T-cell activation in Wegener's granulomatosis. *J Allergy Clin Immunol* 1999; **103**: 885.
20. Keogh KA, Ytterberg SR, Fervenza FC, Carlson KA, Schroeder DR, Specks U. Rituximab for refractory Wegener's granulomatosis: report of a prospective, open-label pilot trial. *Am J Respir Crit Care Med* 2006; **173**: 180.
21. Sailler L. Rituximab off label use for difficult-to-treat auto-immune diseases: reappraisal of benefits and risks. *Clin Rev Allergy Immunol* 2008; **34**: 103.
22. Kallenberg CG. Pathogenesis of PR3–ANCA associated vasculitis. *J Autoimmun* 2008; **30**: 29.
23. Stasi R, Stipa E, Del Poeta G, Amadori S, Newland AC, Provan D. Long-term observation of patients with antineutrophil cytoplasmic antibody-associated vasculitis treated with rituximab. *Rheumatology (Oxford)* 2006; **45**: 1432.
24. Hermle T, Goestemeyer AK, Sweny P, Burns A. Successful therapeutic use of rituximab in refractory Wegener's granulomatosis after renal transplantation. *Clin Nephrol* 2007; **68**: 322.

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