ANCA-associated vasculitis: On clinical management and renal outcome

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SUMMARY AND GENERAL DISCUSSION

CHANGED CLINICAL ASPECTS

There were some recent changes in the daily practice of antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) patients. Indirect immunofluorescence (IIF) for the detection of ANCA is not standardly used anymore. Recent study showed a large variability between different IIF methods and a high diagnostic performance of proteinase (PR3)-ANCA and myeloperoxidase (MPO)-ANCA by Enzyme-Linked Immuno Sorbent Assay (ELISA). Therefore, the use of both IIF and ELISA testing of each sample is not necessary for maximal diagnostic accuracy.[1] Currently a biopsy is still the golden standard for obtaining a diagnosis. In case a biopsy is not possible or should be delayed, a presumptive diagnosis of AAV can be made in case there is a high probability of AAV based on the clinical presentation, ANCA positivity with ELISA and a low suspicion for another disease. With a presumptive diagnosis, initial therapy can be started, although a biopsy should be obtained as soon as possible to confirm the diagnosis.

The approach for initial therapy is based on the severity of the disease and the organs involved. In case of non-organ-threatening and non-life-threatening disease, i.e. in the absence of active glomerulonephritis, pulmonary hemorrhage etc., a regimen with glucocorticoids and methotrexate can be given. Rituximab or cyclophosphamide can be chosen instead of methotrexate. In case of organ-threatening or life-threatening disease glucocorticoids in combination with cyclophosphamide or rituximab can be started. In case of rapidly deteriorating kidney function, severe kidney dysfunction, pulmonary hemorrhage or severe respiratory impairment, adjunctive plasma exchange therapy is advised. Depending on local protocol, prophylaxis against opportunistic infections during induction therapy is given, i.e. trimethoprim-sulfamethoxazole.[2] For maintenance therapy glucocorticoids in combination with azathioprine or methotrexate are mostly used, although rituximab is also being investigated as maintenance therapy in the MAINRITSAN trial[3] and the RITAZAREM trial (RITAZAREM, ClinicalTrials.gov Identifier: NCT01697267). The MAINRITSAN trial showed that at 28 months more patients had remained in remission with rituximab compared to azathioprine. There was no difference in severe adverse events.[3] The optimal duration for maintenance therapy was investigated in the REMAIN trial. This study showed that 48 months of maintenance therapy (azathioprine and prednisolone) had less relapses and an improved renal survival at 48 months compared to 24 months maintenance therapy. There was no difference in the incidence or severity of adverse events or patient survival between both groups.[4] There is still controversy about the duration of glucocorticoids use.

ANTI-PLASMINOGEN AUTOANTIBODIES

It is a big challenge in AAV to detect the presence of anti-plasminogen autoantibodies (α-PLG). We developed an optimized ELISA for the detection of α-PLG, focusing on its usefulness in studies on AAV. We tested different assay set-ups. Purified lysine-plasminogen (lys-PLG) showed better differentiation between positive samples and negative samples compared to glutamic acid-plasminogen (glu-PLG). Therefore, lys-PLG was used as coating antigen. With the optimized α-PLG ELISA we found the presence of α-PLG in 14.3% of MPO-ANCA patients, whereas all our PR3-ANCA patients tested negative in our newly developed assay.

The available studies on α-PLG show a discrepancy in the presence of these autoantibodies in patients with AAV. We mainly detected α-PLG in MPO-ANCA patients, while others detected these antibodies mainly in PR3-ANCA patients or in both patient groups. These discrepancies could be due to differences in the assays used in the studies.[5-7] Examples of differences are different concentrations of coating antigen, different conjugates, different samples (sera vs. purified immunoglobulin G), and different definitions of positivity. We have combined important technical findings and methods from the previous studies which have led to the optimized α-PLG assay presented in chapter 2 of this thesis.

There are two main conformations of PLG, namely glu-PLG and lys-PLG, with glu-PLG being the native form. Lys-PLG is formed after cleavage of a peptide consisting of 77 amino acids at the N-terminal of glu-PLG and is an intermediate step towards the formation of active plasmin.[8] Both conformations differ in physical and functional properties.[9-11] Lys-PLG is more efficiently activated by PLG activators than glu-PLG.[12-14] The different studies on α-PLG published so far did not define which subtype of PLG was used for coating. For the assay developed by us, we used lys-PLG as coating, because it was better at differentiating between positive and negative control samples in our study.

The epitope(s) recognized by α-PLG in AAV are not yet fully defined. Different autoantibodies against different (conformational) epitopes of PLG may exist and this could (partly) explain the described discrepancies. Originally, α-PLG were described in view of anti-complementary PR3 antibodies which were suggested to develop within an idiotypic/anti-idiotypic antibody response.[5,15] Dual reactivity to PLG and complementary PR3 (cPR3) was described in PR3-ANCA patients.[5] This scenario assumed a combined presence of α-PLG with only PR3-ANCA and not MPO-ANCA. The cPR3 sequence has similarities with genetic sequences of microbial and fungal

organisms that code for peptides large enough to be antigenic.[15] If exogenous antigens like peptides of micro-organisms cause the development of autoantibodies against PLG, distinct geographic areas with different micro-organisms could influence the development of these autoantibodies. On the other hand, our study together with those of Berden *et al*. and Hao *et al*. reported the presence of α-PLG in MPO-ANCA patients in the absence of PR3-ANCA.[6,7] This makes the hypothesis regarding cPR3 and α-PLG less likely. In addition, some studies describe α-PLG which did not react to denatured PLG, plasmin or thrombin, while other studies showed cross-reactivity of antibodies between PLG, plasmin and prothrombin.[5,6,16-18] More knowledge about pathogenic epitopes is needed for further optimization of the α-PLG assay and to detect relevant autoantibodies in patients. In the meantime, our currently proposed α-PLG assay can be used for research purposes and further optimization.

The presence of α-PLG is associated with the presence of more active renal lesions in the biopsy, i.e. fibrinoid necrosis and cellular crescents, and worse renal function at 1 year follow-up.[6] The idea is that fibrinoid necrosis is a product of a flaw in the vascular repair system that fails to remove the fibrin clot caused by the vascular injury.[19-23] This flaw is caused by the inhibition of PLG due to α-PLG. In addition, the leaked fibrin seems to stimulate extracapillary proliferation.[24-26] This shows that the presence of these antibodies has an influence on the severity of renal involvement. Therefore, detecting these patients early with a validated α-PLG assay will help improve clinical management of these patients with an improved renal outcome.

PREDICTION OF RENAL RELAPSE

One of the main questions in daily practice when confronted with patients with AAV is how to recognize those who are at risk for disease relapse and whether relapses can be prevented. Identifying patients at high risk of renal relapse may aid in optimizing clinical management. Our study on risk factors for renal disease relapse showed that the histopathological class of ANCA-associated glomerulonephritis (AAGN) and the absence/presence of interstitial inflammatory infiltrates in the renal biopsy at diagnosis are risk factors for renal relapse. More specifically, sclerotic class is associated with a higher rate of renal relapse during long-term follow-up and the absence of interstitial inflammatory infiltrates is associated with the risk of renal relapse.

Previous European Vasculitis Society (EUVAS) studies focused on predictive clinical and serological parameters for relapse in general. Predictive parameters described in the literature are the presence of PR3-ANCA, lower serum creatinine levels at presentation, lung or cardiovascular involvement, and diagnosis of GPA.[27-37] Our

finding that the absence of interstitial infiltrates in renal biopsies predicts renal disease relapse is in line with better renal function increasing the risk for a relapse in general, because absence of interstitial infiltrates also correlates with better renal function at the time of biopsy.[38,39] Interestingly, in a cohort of 535 patients, no clinical parameter at baseline was associated with developing renal relapse.[40] Our study showed histological parameters at baseline that are risk factors for developing renal relapse. A clinical manifestation that is described to be predictive of renal relapse is persistent hematuria during follow-up.[41] Experiencing a renal disease relapse has a negative influence on renal outcome and is associated with end-stage renal failure (ESRF).[40,42] Therefore, clinicians should realize that renal disease relapses must be identified and treated as such.

In the sclerotic class most glomeruli are non-functioning with a decreased compensatory ability of the kidneys. Therefore, renal relapse may become more readily apparent and the functioning glomeruli may become more vulnerable to a second hit, i.e. a relapse. In the focal, crescentic and mixed class, minor relapses may remain subclinical. Patients with interstitial infiltrates (acute disease activity), have a more aggressive clinical disease presentation, making it easier to diagnose the disease early. Treatment will be started earlier and can therefore decrease the risk for renal disease relapse. Therefore, clinicians must keep in mind that those patients with a presumably benign clinical course at onset in particular might be prone to developing a renal disease relapse.

We hypothesize that patients may have smoldering disease in the kidney in which renal relapses may go by unnoticed in case of focal, crescentic and mixed class AAGN. This phenomenon has been described in systemic lupus erythematosus patients after renal transplantation, where subclinical class I, II or III recurrences in the kidney have been encountered unexpectedly in protocol biopsies of 22 patients from a total cohort of 41 patients.[43] Smoldering progression of disease may be devastating to the graft.[43,44] Smoldering disease in general and specifically in the upper and lower airways in AAV has been described.[45-47] In addition, autopsy studies in patients with AAV/GPA showed that persistent airway inflammation is more common than has been appreciated clinically.[48] In our study cohort several patients achieved remission, did not experience a renal disease relapse, but still developed ESRF after achieving remission. In these patients ESRF could be the result of smoldering disease with subclinical renal relapses.

It is also possible that the histopathological classes represent distinct autoimmune syndromes, rather than representing phases according to which the disease progresses.

In our cohort the ANCA-specificity was associated with the histopathologic class. PR3-ANCA was associated with focal class biopsies and MPO-ANCA was associated with sclerotic class. A recent genome-wide association study and meta-analysis in AAV showed that the pathogenesis of AAV has a genetic component. The differences found between GPA and microscopic polyangiitis (MPA) regarding genetic associations were driven by ANCA-specificity and not by clinically defined syndromes. So, PR3–AAV and MPO-AAV seem to have distinct genetic backgrounds and this supports the concept that PR3-AAV and MPO-AAV might be two distinct autoimmune syndromes.[49,50]

HISTOPATHOLOGICAL CLASSIFICATION OF ANCA-ASSOCIATED GLOMERULONEPHRITIS

Several studies described an association between renal histological parameters and renal outcome, for example percentage of normal glomeruli, crescentic glomeruli and sclerotic glomeruli.[38,39,51,52] This led to the introduction of a histopathological classification of AAGN in 2010.[53] This classification classifies each diagnostic renal biopsy into one of four classes; focal, crescentic, sclerotic and mixed class, based on the predominant glomerular phenotype. The first validation of this classification system in 100 patients showed an association with ESRD and renal function at 1- and 5-year follow-up.[53] Several subsequent validation studies confirmed this association regarding focal and sclerotic class, but had contradictory results regarding crescentic and mixed class.[54] Our worldwide validation study also confirmed a favorable outcome in the focal class and a poor outcome in the sclerotic class. Regarding crescentic and mixed class, there was no difference between renal outcome. This is in contrast to the findings of the original study, but is in line with results from 2 recent meta-analyses.[54,55]

The overall histopathological classification showed to be associated with renal function, even after correcting for other baseline parameters, and the development of ESRD during follow-up. However, the crescentic and mixed class were indiscriminate regarding renal function and developing ESRD. There are different possible explanations for these conflicting results regarding crescentic and mixed class. First, there could be differences between the patient populations studied. GPA, MPA and ANCA-specificity are differently distributed around the globe.[56,57] Our validation study showed that the histopathological class and diagnosis are associated with each other, and both variables are associated with renal outcome. Together, differences in patient population could partly be an explanation for the conflicting results. Unfortunately, our cohort was not large enough to analyze this hypothesis. Second, treatment regimens could be different between the patients in the different validation studies. Third, the interobserver agreement between nephropathologists was moderate in

our validation study. It is hard to translate this finding to the clinical practice in a one-on-one fashion, because of the differences in experience, but scoring the same diagnostic biopsy differently can cause the observed differences between the studies. Fourth, the current classification only incorporates normal, crescentic and sclerotic glomeruli. Adding other histological parameters could possibly refine the classification system. Fibrous crescents are not yet incorporated, although they showed to have some predictive value for long-term renal outcome.[39,58] In addition, tubulointerstitial parameters are not considered in the current histopathologic classification of AAGN, while histological studies showed that tubulointerstitial parameters have an association with renal outcome, even when used in addition to the histopathologic classification of AAGN.[38,39,58-67] Our study on renal relapse (chapter 3) and our validation study (chapter 4) confirmed this association.[68] Including tubulointerstitial parameters in the classification system might lead to refinements for the prognostication of patients at time of diagnosis.

The histopathological classification of AAGN is a valuable tool in the management of patients with AAV, but in the near future, adjustments are needed to improve its prognostic value, especially for the crescentic and mixed class. We are not considering to lump the crescentic and mixed class, in particular because other studies showed that cellular crescents are an important factor for predicting potential reversibility of renal impairment during follow-up.[38,39,53] Adding tubulointerstitial parameters could lead to refinements for the prognostication of patients at time of diagnosis, although the poor to moderate interobserver agreement regarding tubulointerstitial variables must also be considered. Currently, we are performing a study to evaluate a more detailed scoring system for both glomerular and interstitial variables. Results from that study will determine how to adjust the histopathological classification for AAGN for more sophisticated prognostic value.

RENAL TRANSPLANTATION

Approximately 20-40% of patients with AAGN progress, with or without clinically evident renal disease relapse, to ESRF.[27,47,69,70] One of the therapeutic options for these patients is a renal transplantation. The Dutch cohort described in this thesis of 113 AAGN patients transplanted between 1984 and 2011 showed one year and five year graft survival rates of 94.5% and 82.8%, respectively. This is similar to previous studies on AAGN and to the general transplantation population in Europe and North America.[71-80] The risk of experiencing a first disease relapse or renal disease recurrence within five years of transplantation was 3.3% and 2.8% per patient year, respectively. This is slightly higher compared to other studies, which described rates of 1.0-2.0%

per patient year.[72,73,75,79,81] Renal disease recurrence was an important cause of graft loss within the first five years after transplantation. Renal transplantation is a viable treatment option for patients with ESRF due to AAGN with rather low renal disease recurrence rates, but once renal disease recurrence has occurred the risk for graft loss is considerable.

The DUTRAVAS study showed that disease recurrence in the renal graft can occur at any time after transplantation. The first disease recurrence in the renal graft occurred nine days after transplantation. This patient was transplanted with ongoing disease activity, which explains the early recurrence. One patient even had a disease recurrence in the renal graft after 142 months. Early (even within days after transplantation, although transplanted during disease remission) and late recurrences of AAGN in the graft have also been described by others.[82-85] This supports that disease recurrence in the renal graft can occur at any time after transplantation. In case of deterioration of renal function, proteinuria and hematuria, even several years after transplantation, disease recurrence in the renal graft should be considered. Continuous and careful monitoring of these patients is important.

An important clinical question with no current formal consensus is time to renal transplantation after reaching clinical remission. A questionnaire sent out by Little *et al.* to transplant units in different countries revealed that 100% of the transplant physicians consulted (n=32) claim that a patient should be in remission at the moment of transplantation.[75] One patient in our cohort was transplanted with ongoing disease activity, had a renal disease recurrence and consequent graft loss within a month. An association between renal transplantation <12 months after reaching clinical remission and mortality was reported.[75] No association was found between the duration of remission before transplantation and disease relapse when taking three months of remission as a cut-off point.[72] However, current practice seems to be delaying the transplantation until the disease is in remission.[73,75,86,87]

Another important question regarding renal transplantation in AAV is whether a patient with a positive ANCA-test can be transplanted. There is still controversy whether a patient must be ANCA negative at the moment of transplantation.[75] Evidence is accumulating that patients with a positive ANCA can be transplanted.[69,72,73,86-92] A paper in 2013 pooled different studies and described an association between ANCA positivity at transplantation and relapse rate, although they mention very scarce information about how they pooled and analyzed these data.[84] The DUTRAVAS study shows that ANCA status at transplantation is not associated with renal disease recurrence and

graft survival. The number of patients in the cohort was too small to discuss PR3-ANCA and MPO-ANCA separately. Therefore, it seems that ANCA positivity at transplantation is not predictive for disease relapse and/or graft loss, which suggests that a patient with a positive ANCA can be transplanted safely. More research on this aspect is needed.

In the DUTRAVAS-study, 36% (4/11) of the patients with disease recurrence in the renal graft lost their graft due to the recurrence within five years after transplantation. Renal disease recurrence in the graft was an important cause of graft loss in this study; four of the 16 graft losses. Graft loss due to AAV recurrence in the graft has also been described in other studies; range 18-60%.[75,85,87,89,91] Briganti *et al*. described a cohort of 1505 patients with biopsy-proven glomerulonephritis due to various causes transplanted between 1988 and 1997 in which at one, five and 10 years after transplantation, recurrent glomerulonephritis was the third most common cause of graft loss. Acute rejection, chronic rejection and death with a functioning graft were more common. In the subgroup analysis, the same order of causes of graft loss was found at 10 years for the pauci-immune crescentic glomerulonephritis patients.[93] Concluding, renal disease recurrence is an important cause of graft loss and the risk for graft loss due to disease recurrence is something clinicians must be aware of.

FUTURE ISSUES

Although a substantial amount of research has been performed and much insight in AAV has been gained, there are still many questions for future research.

One of the clinical challenges in the care of AAV is to predict which patients will have a (renal) relapse of the disease. As literature and our study showed, clinical parameters and histologic lesions in the renal biopsy (glomerular and interstitial) might be of value for this. Future research should focus on specifying these predictors and investigating whether the current histopathological classification of AAGN needs adaptations. These clinical and histological parameters can help the clinician in determining the right therapy.

The use of ANCA titer to predict the course of disease, i.e. disease relapse, and measure current disease activity is controversial. A biomarker which can help the clinician regarding disease course would be very helpful for the clinical management. Therefore, the search for a biomarker should continue. α-PLG, as described in this thesis, has the potential to become such a biomarker to some extent. Other potential biomarkers described in the literature that need further research are B-cells, cytokines,

complement, inflammatory mediators (CXCL13, MMP-3, TIMP-1),[94] hLAMP-2 and urinary biomarkers (MCP1, CD 164, CD 25).[95]

One of the main questions regarding renal transplantation in AAV is how long a patient should be in remission before being transplanted. Currently there is only weak evidence that we should wait for at least one year.[75] The ideal way to answer this question would be an international randomized clinical trial (RCT) of countries with the same organ donor system in which patients are transplanted after different remission times.

There has to be a balance between the risk for adverse events due to the therapy and the chance for disease relapse. The last one still being a big challenge to prevent and treat in AAV. The risk for disease relapse has not changed much for the last few decades.[41] Currently, rituximab with longterm maintenance therapy seems the best option to treat disease relapse, although more research is needed in this field with a RCT specifically focusing on patients with a severe disease relapse. It is also investigated how to taper corticosteroid therapy.

An interesting therapeutic target is the complement system. A randomized trial showed that C5a receptor inhibition with avacopan was an effective treatment in replacing high-dose glucocorticoids in treating AAV patients with newly diagnosed or relapsing disease.[96]

Based on the different genetic background of PR3-ANCA and MPO-ANCA, it remains the question whether these two are different disease modalities and whether they should be treated differently. Until now PR3-ANCA and MPO-ANCA have been treated the same way. These insights will provide us the opportunity to provide better patient-tailored therapy.

REFERENCES

1. Damoiseaux J, Csernok E, Rasmussen N, et al. Detection of antineutrophil cytoplasmic antibodies (ANCAs): a multicentre European Vasculitis Study Group (EUVAS) evaluation of the value of indirect immunofluorescence (IIF) versus antigen-specific immunoassays. *Ann Rheum Dis,* 2016;76(4): 647-653.
2. Merkel PA, Kaplan AA, Falk RJ. Initial immunosuppressive therapy in granulomatosis with polyangiitis and microscopic polyangiitis. *Up To Date,* 2019.
3. Guillevin L, Pagnoux C, Karras A, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med,* 2014;371(19): 1771-1780.
4. Karras A, Pagnoux C, Haubitz M, et al. Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis. *Ann Rheum Dis,* 2017;76(10): 1662-1668.
5. Bautz DJ, Preston GA, Lionaki S, et al. Antibodies with dual reactivity to plasminogen and complementary PR3 in PR3-ANCA vasculitis. *J Am Soc Nephrol,* 2008;19(12): 2421-2429.
6. Berden AE, Nolan SL, Morris HL, et al. Anti-plasminogen antibodies compromise fibrinolysis and associate with renal histology in ANCA-associated vasculitis. *J Am Soc Nephrol,* 2010;21(12): 2169-2179.
7. Hao J, Wang C, Gou SJ, Zhao MH, Chen M. The association between anti-plasminogen antibodies and disease activity in ANCA-associated vasculitis. *Rheumatology (Oxford),* 2014;53(2): 300-306.
8. Zhang L, Gong Y, Grella DK, Castellino FJ, Miles LA. Endogenous plasmin converts Glu-plasminogen to Lys-plasminogen on the monocytoid cell surface. *J Thromb Haemost,* 2003;1(6): 1264-1270.
9. Claeys H, Vermylen J. Physico-chemical and proenzyme properties of NH2-terminal glutamic acid and NH2-terminal lysine human plasminogen. Influence of 6-aminohexanoic acid. *Biochim Biophys Acta,* 1974;342(2): 351-359.
10. Thorsen S, Mullertz S. Rate of activation and electrophoretic mobility of unmodified and partially degraded plasminogen. Effects of 6-aminohexanoic acid and related compounds. *Scand J Clin Lab Invest,* 1974;34(2): 167-176.
11. Violand BN, Sodetz JM, Castellino FJ. The effect of epsilon-amino caproic acid on the gross conformation of plasminogen and plasmin. *Arch Biochem Biophys,* 1975;170(1): 300-305.
12. Hoylaerts M, Rijken DC, Lijnen HR, Collen D. Kinetics of the activation of plasminogen by human tissue plasminogen activator. Role of fibrin. *J Biol Chem,* 1982;257(6): 2912-2919.
13. Markus G, Evers JL, Hobika GH. Comparison of some properties of native (Glu) and modified (Lys) human plasminogen. *J Biol Chem,* 1978;253(3): 733-739.
14. Markus G, Priore RL, Wissler FC. The binding of tranexamic acid to native (Glu) and modified (Lys) human plasminogen and its effect on conformation. *J Biol Chem,* 1979;254(4): 1211-1216.
15. Pendergraft III WF, Preston GA, Shah RR, et al. Autoimmunity is triggered by cPR-3(105-201), a protein complementary to human autoantigen proteinase-3. *Nat Med,* 2004;10(1): 72-79.
16. Puurunen M, Manttari M, Manninen V, Palosuo T, Vaarala O. Antibodies to prothrombin crossreact with plasminogen in patients developing myocardial infarction. *Br J Haematol,* 1998;100(2): 374-379.

17. Puurunen M, Palosuo T, Lassila R, Anttila M, Vaarala O. Immunologic and hematologic properties of antibodies to prothrombin and plasminogen in a mouse model. *Lupus,* 2001;10(2): 108-115.
18. Yang CD, Hwang KK, Yan W, et al. Identification of anti-plasmin antibodies in the antiphospholipid syndrome that inhibit degradation of fibrin. *J Immunol,* 2004;172(9): 5765-5773.
19. Bajema IM. *Aspects of ANCA-associated glomerulonephritis* [PhD thesis]. Leiden, The Netherlands, Leiden University; 2000.
20. Collen A. *Fibrin matrix structure and angiogenesis* [PhD thesis]. Leiden, The Netherlands, Leiden University; 2000.
21. Jennette JC, Wilkman AS, Falk RJ. Anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis and vasculitis. *Am J Pathol,* 1989;135(5): 921-930.
22. Novak RF, Christiansen RG, Sorensen ET. The acute vasculitis of Wegener's granulomatosis in renal biopsies. *Am J Clin Pathol,* 1982;78(3): 367-371.
23. Serra A, Cameron JS, Turner DR, et al. Vasculitis affecting the kidney: presentation, histopathology and long-term outcome. *Q J Med,* 1984;53(210): 181-207.
24. Channing AA, Kasuga T, Horowitz RE, Dubois EL, Demopoulos HB. An ultrastructural study of spontaneous lupus nephritis in the NZB-BL-NZW mouse. *Am J Pathol,* 1965;47(4): 677-694.
25. Silva FG, Hoyer JR, Pirani CL. Sequential studies of glomerular crescent formation in rats with antiglomerular basement membrane-induced glomerulonephritis and the role of coagulation factors. *Lab Invest,* 1984;51(4): 404-415.
26. Vassalli P, McCluskey RT. The Pathogenic Role of the Coagulation Process in Rabbit Masugi Nephritis. *Am J Pathol,* 1964;45: 653-677.
27. Booth AD, Almond MK, Burns A, et al. Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. *Am J Kidney Dis,* 2003;41(4): 776-784.
28. Harper L, Morgan MD, Walsh M, et al. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. *Ann Rheum Dis,* 2012;71(6): 955-960.
29. 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(9): 621-631.
30. Jayne D, Rasmussen N, Andrassy K, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med,* 2003;349(1): 36-44.
31. Koldingsnes W, Nossent JC. Baseline features and initial treatment as predictors of remission and relapse in Wegener's granulomatosis. *J Rheumatol,* 2003;30(1): 80-88.
32. Kyndt X, Reumaux D, Bridoux F, et al. Serial measurements of antineutrophil cytoplasmic autoantibodies in patients with systemic vasculitis. *Am J Med,* 1999;106(5): 527-533.
33. Lionaki S, Blyth ER, Hogan SL, et al. Classification of antineutrophil cytoplasmic autoantibody vasculitides: the role of antineutrophil cytoplasmic autoantibody specificity for myeloperoxidase or proteinase 3 in disease recognition and prognosis. *Arthritis Rheum,* 2012;64(10): 3452-3462.
34. Pagnoux C, Hogan SL, Chin H, et al. Predictors of treatment resistance and relapse in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis: comparison of two independent cohorts. *Arthritis Rheum,* 2008;58(9): 2908-2918.

35. Salmela A, Tornroth T, Poussa T, Ekstrand A. Prognostic Factors for Survival and Relapse in ANCA-Associated Vasculitis with Renal Involvement: A Clinical Long-Term Follow-Up Study. *Int J Nephrol,* 2018: 6369814.
36. Stegeman CA, Cohen Tervaert JW, Sluiter WJ, Manson WL, De Jong PE, Kallenberg CGM. Association of chronic nasal carriage of Staphylococcus aureus and higher relapse rates in Wegener granulomatosis. *Ann Intern Med,* 1994;120(1): 12-17.
37. Walsh M, Flossmann O, Berden A, et al. Risk factors for relapse of antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum,* 2012;64(2): 542-548.
38. Bajema IM, Hagen EC, Hermans J, et al. Kidney biopsy as a predictor for renal outcome in ANCA-associated necrotizing glomerulonephritis. *Kidney Int,* 1999;56(5): 1751-1758.
39. Hauer HA, Bajema IM, Van Houwelingen HC, et al. Determinants of outcome in ANCA-associated glomerulonephritis: a prospective clinico-histopathological analysis of 96 patients. *Kidney Int,* 2002;62(5): 1732-1742.
40. Wester Trejo MAC, Flossmann O, Westman KW, et al. Renal relapse in antineutrophil cytoplasmic autoantibody-associated vasculitis: unpredictable, but predictive of renal outcome. *Rheumatology (Oxford),* 2019;58(1): 103-109.
41. Rhee RL, Hogan SL, Poulton CJ, et al. Trends in Long-Term Outcomes Among Patients With Antineutrophil Cytoplasmic Antibody-Associated Vasculitis With Renal Disease. *Arthritis Rheumatol,* 2016;68(7): 1711-1720.
42. de Joode AA, Sanders JS, Stegeman CA. Renal survival in proteinase 3 and myeloperoxidase ANCA-associated systemic vasculitis. *Clin J Am Soc Nephrol,* 2013;8(10): 1709-1717.
43. Norby GE, Strom EH, Midtvedt K, et al. Recurrent lupus nephritis after kidney transplantation: a surveillance biopsy study. *Ann Rheum Dis,* 2010;69(8): 1484-1487.
44. Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol,* 2004;15(2): 241-250.
45. Mark EJ, Flieder DB, Matsubara O. Treated Wegener's granulomatosis: distinctive pathological findings in the lungs of 20 patients and what they tell us about the natural history of the disease. *Hum Pathol,* 1997;28(4): 450-458.
46. Voswinkel J, Mueller A, Kraemer JA, et al. B lymphocyte maturation in Wegener's granulomatosis: a comparative analysis of VH genes from endonasal lesions. *Ann Rheum Dis,* 2006;65(7): 859-864.
47. Westman KWA, Bygren PG, Olsson H, Ranstam J, Wieslander J. Relapse rate, renal survival, and cancer morbidity in patients with Wegener's granulomatosis or microscopic polyangiitis with renal involvement. *J Am Soc Nephrol,* 1998;9(5): 842-852.
48. Bacon PA. The spectrum of Wegener's granulomatosis and disease relapse. *N Engl J Med,* 2005;352(4): 330-332.
49. Lyons PA, Rayner TF, Trivedi S, et al. Genetically distinct subsets within ANCA-associated vasculitis. *N Engl J Med,* 2012;367(3): 214-223.
50. Rahmattulla C, Mooyaart AL, van Hooven D, et al. Genetic variants in ANCA-associated vasculitis: a meta-analysis. *Ann Rheum Dis,* 2015;75: 1687-1692.
51. Aasarod K, Bostad L, Hammerstrom J, Jorstad S, Iversen BM. Renal histopathology and clinical course in 94 patients with Wegener's granulomatosis. *Nephrol Dial Transplant,* 2001;16(5): 953-960.

52. Haroun MK, Stone JH, Nair R, Racusen L, Hellmann DB, Eustace JA. Correlation of percentage of normal glomeruli with renal outcome in Wegener's granulomatosis. *Am J Nephrol,* 2002;22(5-6): 497-503.
53. Berden AE, Ferrario F, Hagen EC, et al. Histopathologic classification of ANCA-associated glomerulonephritis. *J Am Soc Nephrol,* 2010;21(10): 1628-1636.
54. Chen YX, Xu J, Pan XX, et al. Histopathological Classification and Renal Outcome in Patients with Antineutrophil Cytoplasmic Antibodies-associated Renal Vasculitis: A Study of 186 Patients and Metaanalysis. *J Rheumatol,* 2017;44(3): 304-313.
55. Huang S, Shen Q, Yang R, Lai H, Zhang J. An evaluation of the 2010 histopathological classification of anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis: a Bayesian network meta-analysis. *Int Urol Nephrol,* 2018;50(10): 1853-1861.
56. Watts RA, Lane SE, Scott DG, et al. Epidemiology of vasculitis in Europe. *Ann Rheum Dis,* 2001;60(12): 1156-1157.
57. Watts RA, Scott DG, Jayne DR, et al. Renal vasculitis in Japan and the UK--are there differences in epidemiology and clinical phenotype? *Nephrol Dial Transplant,* 2008;23(12): 3928-3931.
58. de Lind van Wijngaarden RAF, Hauer HA, Wolterbeek R, et al. Clinical and histologic determinants of renal outcome in ANCA-associated vasculitis: a prospective analysis of 100 patients with severe renal involvement. *J Am Soc Nephrol,* 2006;17(8): 2264-2274.
59. Berden AE, Jones RB, Erasmus DD, et al. Tubular lesions predict renal outcome in antineutrophil cytoplasmic antibody-associated glomerulonephritis after rituximab therapy. *J Am Soc Nephrol,* 2012;23(2): 313-321.
60. Brix SR, Noriega M, Tennstedt P, et al. Development and validation of a renal risk score in ANCA-associated glomerulonephritis. *Kidney Int,* 2018;94(6): 1177-1188.
61. Ford SL, Polkinghorne KR, Longano A, et al. Histopathologic and clinical predictors of kidney outcomes in ANCA-associated vasculitis. *Am J Kidney Dis,* 2014;63(2): 227-235.
62. Hogan SL, Nachman PH, Wilkman AS, Jennette JC, Falk RJ, Network GDC. Prognostic markers in patients with antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. *J Am Soc Nephrol,* 1996;7(1): 23-32.
63. Levi C, Meas-Yedid V, Daniliuc C, et al. Computerized Instersitial Fibrosis Is the Most Powerful Histological Predictor of Renal Outcome in ANCA-Associated Vasculitis. *J Am Soc Nephrol,* 2012(23): 710A-711A.
64. Muso E, Endo T, Itabashi M, et al. Evaluation of the newly proposed simplified histological classification in Japanese cohorts of myeloperoxidase-anti-neutrophil cytoplasmic antibody-associated glomerulonephritis in comparison with other Asian and European cohorts. *Clin Exp Nephrol,* 2013;17(5): 659-662.
65. Muso E, Endo T, Yumura W, Joh K. Need of Interstitial Fibrosis Parameter on the Newly Proposed Simplified Glomerular Histological Classification to Predict the Longterm Outcome in Japanese Cohort of MPO-ANCA Associated RPGN. *J Am Soc Nephrol,* 2012(23): 532A-532A.
66. Quintana LF, Perez NS, De SE, et al. ANCA serotype and histopathological classification for the prediction of renal outcome in ANCA-associated glomerulonephritis. *Nephrol Dial Transplant,* 2014;29(9): 1764-1769.

67. Tanna A, Guarino L, Tam FW, et al. Long-term outcome of anti-neutrophil cytoplasm antibody-associated glomerulonephritis: evaluation of the international histological classification and other prognostic factors. *Nephrol Dial Transplant,* 2015;30(7): 1185-1192.
68. Goceroglu A, Berden AE, Fiocco M, et al. ANCA-Associated Glomerulonephritis: Risk Factors for Renal Relapse. *PLoS One,* 2016;11(12): e0165402.
69. Little MA, Nazar L, Farrington K. Outcome in glomerulonephritis due to systemic small vessel vasculitis: effect of functional status and non-vasculitic co-morbidity. *Nephrol Dial Transplant,* 2004;19(2): 356-364.
70. Slot MC, Cohen Tervaert JW, Franssen CFM, Stegeman CA. Renal survival and prognostic factors in patients with PR3-ANCA associated vasculitis with renal involvement. *Kidney Int,* 2003;63(2): 670-677.
71. Cecka JM. The OPTN/UNOS Renal Transplant Registry. *Clin Transpl.* 2005;19:1-16.
72. Geetha D, Eirin A, True K, et al. Renal transplantation in antineutrophil cytoplasmic antibody-associated vasculitis: a multicenter experience. *Transplantation,* 2011;91(12): 1370-1375.
73. 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(12): 1296-1301.
74. Gondos A, Dohler B, Brenner H, Opelz G. Kidney graft survival in Europe and the United States: strikingly different long-term outcomes. *Transplantation,* 2013;95(2): 267-274.
75. Little MA, Hassan B, Jacques S, et al. Renal transplantation in systemic vasculitis: when is it safe? *Nephrol Dial Transplant,* 2009;24(10): 3219-3225.
76. Shen J, Gill J, Shangguan M, Sampaio MS, Bunnapradist S. Outcomes of renal transplantation in recipients with Wegener's granulomatosis. *Clin Transplant,* 2011;25(3): 380-387.
77. Stel VS, van de Luijtgaarden MWM, Wanner C, Jager KJ, Investigators ERR. The 2008 ERA-EDTA Registry Annual Report-a precis. *NDT Plus,* 2011;4(1): 1-13.
78. Tang W, Bose B, McDonald SP, et al. The Outcomes of Patients with ESRD and ANCA-Associated Vasculitis in Australia and New Zealand. *Clin J Am Soc Nephrol,* 2013;8: 773-780.
79. Buttigieg J, Henderson L, Kidder D. Outcome of Kidney Transplant in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. *Exp Clin Transplant,* 2017;15(5): 509-515.
80. Wallace ZS, Wallwork R, Zhang Y, et al. Improved survival with renal transplantation for end-stage renal disease due to granulomatosis with polyangiitis: data from the United States Renal Data System. *Ann Rheum Dis,* 2018;77(9): 1333-1338.
81. Allen A, Pusey C, Gaskin G. Outcome of renal replacement therapy in antineutrophil cytoplasmic antibody-associated systemic vasculitis. *J Am Soc Nephrol,* 1998;9(7): 1258-1263.
82. Fogazzi GB, Banfi G, Allegri L, Bignardi L. Late recurrence of systemic vasculitis after kidney transplantation involving the kidney allograft. *Adv Exp Med Biol,* 1993;336: 503-506.
83. Hadaya K, Marangon N, Moll S, Ferrari-Lacraz S, Villard J. Early relapse of autoimmune glomerulonephritis after kidney transplantation despite antibody induction and triple-drug-based immunosuppression. *Transplantation,* 2010;89(6): 767-769.

84. Marco H, Mirapeix E, Arcos E, et al. Long-term outcome of antineutrophil cytoplasmic antibody-associated small vessel vasculitis after renal transplantation. *Clin Transplant,* 2013;27(3): 338-347.
85. 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(9): 2133-2139.
86. Deegens JK, Artz MA, Hoitsma AJ, Wetzels JF. Outcome of renal transplantation in patients with pauci-immune small vessel vasculitis or anti-GBM disease. *Clin Nephrol,* 2003;59(1): 1-9.
87. Nachman PH, Segelmark M, Westman K, et al. Recurrent ANCA-associated small vessel vasculitis after transplantation: a pooled analysis. *Kidney Int,* 1999;56(4): 1544-1550.
88. Geetha D, Lee SM, Shah S, Rahman HM. Relevance of ANCA positivity at the time of renal transplantation in ANCA associated vasculitis. *J Nephrol,* 2017;30(1): 147-153.
89. Haubitz M, Kliem V, Koch KM, et al. Renal transplantation for patients with autoimmune diseases: single-center experience with 42 patients. *Transplantation,* 1997;63(9): 1251-1257.
90. Nyberg G, Akesson P, Norden G, Wieslander J. Kidney transplantation in patients with systemic vasculitis. *Transplant Proc,* 1997;29(1-2): 235.
91. Nyberg G, Akesson P, Norden G, Wieslander J. Systemic vasculitis in a kidney transplant population. *Transplantation,* 1997;63(9): 1273-1277.
92. Rostaing L, Modesto A, Oksman F, Cisterne JM, Le Mao G, Durand D. Outcome of patients with antineutrophil cytoplasmic autoantibody-associated vasculitis following cadaveric kidney transplantation. *Am J Kidney Dis,* 1997;29(1): 96-102.
93. Briganti EM, Russ GR, McNeil JJ, Atkins RC, Chadban SJ. Risk of renal allograft loss from recurrent glomerulonephritis. *N Engl J Med,* 2002;347(2): 103-109.
94. Monach PA, Warner RL, Tomasson G, et al. Serum proteins reflecting inflammation, injury and repair as biomarkers of disease activity in ANCA-associated vasculitis. *Ann Rheum Dis,* 2013;72(8): 1342-1350.
95. Tedesco M, Gallieni M, Pellegata F, Cozzolino M, Alberici F. Update on ANCA-associated vasculitis: from biomarkers to therapy. *J Nephrol,* 2019;32(6): 871-882.
96. Jayne DR, Bruchfeld AN, Harper L, et al. Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis. *J Am Soc Nephrol,* 2017;28(9): 2756-2767.