PROYECTO PROMETEO2

RECIDIVA DE LA ENFERMEDAD RENAL PRIMARIA

26 y 27 de NOVIEMBRE 2021 MADRID

Dosier Bibliográfico

Grupo III | **Diagnóstico y tratamiento de la recidiva de glomerulopatías C3, glomerulonefritis por inmunocomplejos, nefropatía membranosa, vasculitis, lupus eritematoso sistémico y síndrome antifosfolípico**

Portavoz | **Joana Sellarés e Irina Torres**

Organizado por

SET SOCIEDAD ESPAÑOLA DE TRASPLANTE

Con la colaboración de

SANDOZ A Novartis Division

NOVARTIS

1. RECIDIVA GLOMERULOPATÍA C3 Y GN POR IC

CLASIFICACIÓN Y FISIOPATOLOGÍA

1. Membranoproliferative Glomerulonephritis: Pathogenetic Heterogeneity and Proposal for a New Classification.
Sethi S, Fervenza FC.
Seminars in Nephrology, Vol 31, No 4, July 2011, pp 341-348.

ABSTRACT
Membranoproliferative glomerulonephritis (MPGN) is a pattern of injury that results from subendothelial and mesangial deposition of Igs caused by persistent antigenemia and/or circulating immune complexes. The common causes of Ig-mediated MPGN include chronic infections, autoimmune diseases, and monoclonal gammopathy/dysproteinemias. On the other hand, MPGN also can result from subendothelial and mesangial deposition of complement owing to dysregulation of the alternative pathway (AP) of complement. Complement-mediated MPGN includes dense deposit disease and proliferative glomerulonephritis with C3 deposits. Dysregulation of the AP of complement can result from genetic mutations or development of autoantibodies to complement regulating proteins with ensuing dense deposit disease or glomerulonephritis with C3 deposits. We propose a new histologic classification of MPGN and classify MPGN into 2 major groups: Ig-mediated and complement-mediated. MPGN that is Ig-mediated should lead to work-up for infections, autoimmune diseases, and monoclonal gammopathy. On the other hand, complement-mediated MPGN should lead to work-up of the AP of complement. Initial AP screening tests should include serum membrane attack complex levels, an AP functional assay, and a hemolytic assay, followed by tests for mutations and autoantibodies to complement-regulating proteins.

2. Membranoproliferative Glomerulonephritis — A New Look at an Old Entity.
Sethi S, Fervenza FC.
N Engl J Med 2012;366:1119-31.

No abstract available

3. Pathogenesis of the C3 glomerulopathies and reclassification of MPGN.
Bomback AS, Appel GB.
Nat. Rev. Nephrol. 8, 634–642 (2012).

ABSTRACT
Until recently, membranoproliferative glomerulonephritis (MPGN) was clinically classified as either primary, idiopathic MPGN or as secondary MPGN when an underlying aetiology was identifiable. Primary MPGN was further classified into three types--type I, type II, and type III--based principally on the ultrastructural appearance and location of electron-dense deposits. Both the clinical and histopathologic schemes presented problems, however, as neither was based on disease

pathogenesis. An improved understanding of the role of complement in the pathogenesis of MPGN has led to a proposed reclassification into immunoglobulin-mediated disease (driven by the classical complement pathway) and non-immunoglobulin-mediated disease (driven by the alternative complement pathway). This reclassification has led to improved diagnostic clinical algorithms and the emergence of a new grouping of diseases known as the C3 glomerulopathies, best represented by dense deposit disease and C3 glomerulonephritis. In this Review, we re-examine the previous and current classification schemes of MPGN, focusing on the role of complement. We survey current data about the pathogenesis of the C3 glomerulopathies, including familial studies and patient cohorts from the USA and Europe. In addition, we discuss the diagnosis, treatment, and prognosis of the C3 glomerulopathies.

4. C3 glomerulopathy — understanding a rare complement-driven renal disease.
Smith RJH, Appel GB, Blom AM et al.
Nat Rev Nephrol. 2019 Mar;15(3):129-143

ABSTRACT
The C3 glomerulopathies are a group of rare kidney diseases characterized by complement dysregulation occurring in the fluid phase and in the glomerular microenvironment, which results in prominent complement C3 deposition in kidney biopsy samples. The two major subgroups of C3 glomerulopathy - dense deposit disease (DDD) and C3 glomerulonephritis (C3GN) - have overlapping clinical and pathological features suggestive of a disease continuum. Dysregulation of the complement alternative pathway is fundamental to the manifestations of C3 glomerulopathy, although terminal pathway dysregulation is also common. Disease is driven by acquired factors in most patients - namely, autoantibodies that target the C3 or C5 convertases. These autoantibodies drive complement dysregulation by increasing the half-life of these vital but normally short-lived enzymes. Genetic variation in complement-related genes is a less frequent cause. No disease-specific treatments are available, although immunosuppressive agents and terminal complement pathway blockers are helpful in some patients. Unfortunately, no treatment is universally effective or curative. In aggregate, the limited data on renal transplantation point to a high risk of disease recurrence (both DDD and C3GN) in allograft recipients. Clinical trials are underway to test the efficacy of several first-generation drugs that target the alternative complement pathway.

DIAGNÓSTICO, FACTORES DE RIESGO Y PRONÓSTICO.

5. Recurrent glomerulonephritis after kidney transplantation: risk factors and allograft outcomes.
Chadban SJ, Craig JC, Lim WH et al.
Kidney International (2017) 92, 461–469.

ABSTRACT
Recurrent glomerulonephritis after kidney transplantation is a feared complication because it is unpredictable and may have a negative impact on graft outcomes. To better understand this we

collected data from the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry accumulated over 30 years. The incidence, risk factors, and outcomes of recurrent glomerulonephritis in transplant recipients were determined using adjusted Cox proportional hazard and competing risk modeling. A total of 6,597 recipients with biopsy-proven glomerulonephritis as the primary cause of end-stage kidney disease were followed for 51,871 person-years (median duration 7.7 years). The four most common types of glomerulonephritis were IgA nephropathy in 2501 patients, focal segmental glomerulosclerosis (FSGS) in 1403, membranous in 376, and membranoproliferative (MPGN) nephropathy in 357 patients. Among these four types, recurrence was reported in 479 of 4637 patients, and of these, 212 lost their allograft due to recurrence. Older age at transplantation (adjusted hazard ratio [per year increase] 0.96 [95% confidence interval 0.95 - 0.97]) was associated with a lower risk of recurrence. Significantly, the five-year graft survival was 30% for recipients with recurrent MPGN and 57-59% for recipients with FSGS, IgA, and membranous nephropathy. Transplant recipients with recurrent disease were twice as likely to lose their allografts compared to those without recurrence (adjusted hazard ratio 2.04 [1.81-2.31]). Thus, recurrent glomerulonephritis remains a significant cause of graft loss in transplant recipients.

6. C3 Practical management of C3 glomerulopathy and immunoglobulin-mediated MPGN: facts and uncertainties.

Fakhouri F, Le Quintrec M, Frémeaux-Bacchi V.
Kidney Int. 2020 Jul 2;S0085-2538(20)30721-3.

ABSTRACT
In recent years, a substantial body of experimental and clinical work has been devoted to C3 glomerulopathy and immunoglobulin-mediated membranoproliferative glomerulonephritis. Despite the rapid accumulation of data, several uncertainties regarding these two rare forms of nephropathies persist. They concern their pathophysiology, classification, clinical course, relevance of biomarkers and of pathology findings and assessment of the efficacy of available therapies. The present review discusses the impact of these uncertainties on the clinical management of patients.

7. C3 glomerulopathy: consensus report.

Pickering MC, D'Agati VD, Nester CM.
Kidney International (2013) 84, 1079–1089.

ABSTRACT
C3 glomerulopathy is a recently introduced pathological entity whose original definition was glomerular pathology characterized by C3 accumulation with absent or scanty immunoglobulin deposition. In August 2012, an invited group of experts (comprising the authors of this document) in renal pathology, nephrology, complement biology, and complement therapeutics met to discuss C3 glomerulopathy in the first C3 Glomerulopathy Meeting. The objectives were to reach a consensus on: the definition of C3 glomerulopathy, appropriate complement investigations that should be performed in these patients, and how complement therapeutics should be explored in the condition. This meeting report represents the current consensus view of the group.

8. Clinical findings, pathology, and outcomes of C3GN after kidney transplantation.
Zand L, Lorenz EC, Cosio FG et al.
J Am Soc Nephrol 2014; 25: 1110–1117.

ABSTRACT
C3 glomerulonephritis (C3GN) results from abnormalities in the alternative pathway of complement, and it is characterized by deposition of C3 with absent or scant Ig deposition. In many patients, C3GN progresses to ESRD. The clinical features, pathology, and outcomes of patients with C3GN receiving kidney transplantation are unknown. Between 1996 and 2010, we identified 21 patients at our institution who received a kidney transplant because of ESRD from C3GN. The median age at the time of initial diagnosis of C3GN at kidney biopsy was 20.8 years. The median time from native kidney biopsy to dialysis or transplantation was 42.3 months. Of 21 patients, 14 (66.7%) patients developed recurrent C3GN in the allograft. The median time to recurrence of disease was 28 months. Graft failure occurred in 50% of patients with recurrent C3GN, with a median time of 77 months to graft failure post-transplantation. The remaining 50% of patients had functioning grafts, with a median follow-up of 73.9 months. The majority of patients had hematuria and proteinuria at time of recurrence. Three (21%) patients were positive for monoclonal gammopathy and had a faster rate of recurrence and graft loss. Kidney biopsy at the time of recurrence showed mesangial proliferative GN in eight patients and membranoproliferative GN in six patients. All allograft kidney biopsies showed bright C3 staining (2-3+), with six biopsies also showing trace/1+ staining for IgM and/or IgG. To summarize, C3GN recurs in 66.7% of patients, and one half of the patients experience graft failure caused by recurrence.

9. Advances in the Understanding of Complement Mediated Glomerular Disease: Implications for Recurrence in the Transplant Setting.
Barbour S and Gill JS.
Am J Transplant 2015 Feb;15(2):312-9.

ABSTRACT
Recent advances in the understanding of the role of complement in glomerular disease allow for more accurate assessment of the risk of disease recurrence after transplantation, and inform the development of targeted treatment strategies to overcome specific defects in the alternate pathway of the complement system. These advances along with remaining knowledge deficits are reviewed with specific relevance to membranoproliferative glomerulonephritis (MPGN) and C3 glomerulopathy, a heterogenous group of diseases with a high rate of recurrence leading to allograft failure. Recommendations to establish an accurate diagnosis and inform therapeutic decision making in transplant candidates with a histologic diagnosis of MPGN are provided.

10. Kidney Transplantation in C3 Glomerulopathy: A case Series.
Regunathan-Shenk R, Avasare RS, Ahn W et al.
Am J Kidney Dis. 2019 Mar;73(3):316-323. PMID: 30413277.

ABSTRACT

Rationale & objective: C3 glomerulopathy (C3G), a form of glomerulonephritis associated with dysregulation of the alternative complement pathway, occurs either as dense deposit disease (DDD) or C3 glomerulonephritis (C3GN). Few studies have reported outcomes of patients with C3G after transplantation since its formal classification and the advent of complement-targeting therapies such as eculizumab.
Study design: Case series of C3G.
Setting & participants: We reviewed laboratory testing, native and allograft biopsy reports, and clinical charts of the 19 patients (12, C3GN; and 7, DDD) from our C3G registry who underwent transplantation between 1999 and 2016.
Results: During a median follow-up of 76 months, 16 patients had recurrent disease (10 of 12, C3GN; and 6 of 7, DDD), with median time to recurrence of 14 months in C3GN versus 15 months in DDD. Graft failure was more frequent in patients with DDD (6 of 7) than in patients with C3GN (3 of 12), occurred at a median time of 42 months posttransplantation, and was attributed to recurrent disease in half the failures. A rare genetic variant or autoantibody associated with alternative complement pathway abnormalities was detected in 9 of 10 screened patients. Treatment of 7 patients (8 allografts) with eculizumab was associated with variable clinical outcomes.
Limitations: Incomplete testing for complement pathway abnormalities and genetic defects, incomplete records of HLA antigen matching, lack of centralized biopsy review, and limited sample size.
Conclusions: In a case series of C3G transplant recipients, the proportion of disease recurrence was high in both C3GN and DDD, although graft loss appeared to occur more frequently in DDD. In a small subset of study patients, eculizumab therapy was not consistently followed by salutary outcomes.

11. C4d as a Diagnostic Tool in Proliferative GN.

Sethi S, Nasr SH, De Vriese AS et al.
J Am Soc Nephrol 26: 2852–2859, 2015.

ABSTRACT
Proliferative GN is classified as immune complex-mediated or complement-mediated (C3 glomerulopathy). Immune complex-mediated GN results from glomerular deposition of immune-complexes/Ig and C3; the C3 is derived from activation of the classical and/or lectin pathways of complement. C3 glomerulopathy results from deposition of C3 and other complement fragments with minimal or no deposition of immune complexes/Ig; the C3 is derived from activation of the alternative pathway of complement. C4d is a byproduct of activation of the classic and lectin pathways. Although widely used as a marker for antibody-mediated rejection, the significance of C4d in C3 glomerulopathy is undetermined. We studied glomerular C4d staining in 18 biopsy specimens of immune-complex GN, 30 biopsy specimens of C3 GN, and 13 biopsy specimens of postinfectious GN. All specimens of immune complex-mediated GN, except two specimens of IgA nephropathy and one specimen of sclerosing membranoproliferative GN, showed bright (2-3+) C4d staining. The staining pattern of C4d mirrored the staining patterns of Ig and C3. Conversely, C4d staining was completely negative in 24 (80%) of 30 specimens of C3 glomerulopathy, and only trace/1+ C4d staining was detected in six (20%) specimens. With regard to postinfectious GN, C4d staining was negative in six (46%) of 13 specimens, suggesting an abnormality in the alternative

pathway, and it was positive in seven (54%) specimens. To summarize, C4d serves as a positive marker for immune complex-mediated GN but is absent or minimally detected in C3 glomerulopathy.

12. Complement gene variants determine the risk of immunoglobulin-associated MPGN and C3 glomerulopathy and predict long- term renal outcome.

Iatropoulos P, Noris M, Mele C et al.

Mol Immunol. 2016 Mar;71:131-142.

ABSTRACT

Background: Membranoproliferative glomerulonephritis (MPGN) is an uncommon cause of chronic nephropathy recently reclassified into immunoglobulin-associated MPGN (Ig-MPGN) and C3 glomerulopathy (C3G). In this study we aimed: (1) to evaluate the complement genetic and biochemical profile in patients with Ig-MPGN/C3G; (2) to investigate whether genetic variants and different patterns of complement activation (i.e., fluid versus solid phase) correlate with disease manifestations and outcomes.

Methods: In 140 patients with idiopathic Ig-MPGN or C3G we performed complement biochemical and genetic screening and correlated genetic, biochemical and histology data with clinical features.

Results: Mutations in genes encoding alternative pathway complement proteins were found in both Ig-MPGN and C3G, and mutations in the two components of the C3 convertase are the most prevalent. We also report a mutation in THBD encoding thrombomodulin in a C3G patient. The presence of mutations alone does not significantly increase the risk of Ig-MPGN or C3G, but it does so when combined with common susceptibility variants (CD46 c.-366A in Ig-MPGN; CFH V62 and THBD A473 in C3G). Finally, patients without complement gene mutations or C3NeFs--autoantibodies that stabilize the alternative pathway C3 convertase--have a higher risk of progressing to end-stage renal disease than patients with identified mutations and/or C3NeFs, suggesting the existence of different pathogenetic mechanisms that lead to renal disease.

Conclusions: We provide new insights into the pathogenesis of Ig-MPGN/C3G that underscore the complex nature of these diseases and suggest that the current C3G classification may miss many cases associated with abnormalities of the complement alternative pathway.

13. Allograft failure in kidney transplant recipients with membranoproliferative glomerulonephritis.

Angelo J R, Bell CS, Braun MC.

Am. J. Kidney Dis. 57, 291–299 (2011).

ABSTRACT

Background: Membranoproliferative glomerulonephritis types I (MPGN-I) and II (MPGN-II) are rare diseases that in limited case series have been reported to recur frequently in kidney transplants and have a negative impact on allograft survival.

Study design: Retrospective database review.

Setting & participants: 189,211 primary kidney transplants in the United Network for Organ Sharing (UNOS) database from September 1987 to May 2007.

Predictor or factor: MPGN-I (811 patients; 0.4%), MPGN-II (179 patients; 0.1%), other GN (58,129 patients; 30.7%), and all other diagnoses (130,092 patients; 68.7%).
Outcomes: Death-censored and non-death-censored allograft survival.
Results: Compared with controls, patients with MPGN-I and MPGN-II were significantly younger at the time of transplant, with a median age of 36 and 27 years compared with 44 years in the GN group and 46 years in all other disease groups, respectively (all P < 0.001). Mortality in patients with MPGN-I (8.8%) was significantly lower compared with the GN (11.3%; P = 0.02) and other disease (16.6%; P < 0.001) populations and lower in those with MPGN-II (9.5%) compared with the other disease (16.6%; P = 0.01) population. Graft failure rates were significantly higher in the MPGN-I (44.5%) cohort, but not in the MPGN-II (45.3%) cohort compared with the GN (38.0%) population (P < 0.001 and P = 0.05, respectively); neither MPGN cohort differed from the other disease (43.0%) population (P = 0.4 and P = 0.5). Overall, 10-year death-censored graft survival was similar for MPGN-I (56.2%) and MPGN-II (57.5%); both were significantly worse than for GN (65.2%; P < 0.001 and P = 0.003, respectively), and only MPGN-I was significantly worse than the other disease (60.0%) population (P = 0.004). Of allograft failures with a reported cause, disease recurrence was the primary cause in 36 (14.5%) MPGN-I and 18 (29.5%) MPGN-II transplant recipients and was significantly higher compared with 879 (6.6%) GN and 1,319 (4.4%) all-other-disease recurrence failures (P < 0.001).
Limitations: Limited pretransplant clinical and biopsy data.
Conclusions: A diagnosis of MPGN-I or MPGN-II has a significant negative impact on overall primary allograft survival compared with other forms of glomerulonephritis, whereas only MPGN-I has a significant, but modest, negative effect compared with other causes of end-stage renal disease.

TRATAMIENTO

14. Complete biopsy-proven resolution of deposits in recurrent proliferative glomerulonephritis with monoclonal IgG deposits (PGNMIGD) following rituximab treatment in renal allograft. Jon Von Visger J, Cassol C, Nori U et al.
BMC Nephrol. 2019 Feb 14;20(1):53.

ABSTRACT
Background: Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMIGD) is a disease entity classified under the group of "Monoclonal gammopathy-related kidney diseases", and can recur after transplant. Clinical remission of proteinuria in patients with PGNMIGD has been previously shown following anti-B cell and/or anti-plasma cell therapies. Our case is the first to show complete histologic resolution of the glomerular monoclonal IgG kappa deposits in a case of recurrent PGNMIGD in renal allograft after rituximab and steroid treatment. This is a novel finding and it shows that the deposits are amenable to therapy. This case also highlights the importance of IgG subclass staining in the recognition of the monoclonal nature of the deposits. It is particularly important in PGNMIGD because only 20 to 30% of patients with this disease are reported to have detectable monoclonal gammopathy, and the deposits do not have any organized substructure on electron microscopic examination. Morphologically, they resemble

polyclonal immune-type deposits seen in other immune complex glomerulonephritides such as lupus nephritis, infection-associated glomerulonephritis, and membranoproliferative glomerulonephritis (MPGN type I).

Case presentation: The patient is a 44 year old Caucasian male who received a living unrelated donor kidney transplant for end-stage renal disease diagnosed 7 years before transplant. The reported native kidney biopsy diagnosis was membranoproliferative glomerulonephritis (MPGN) with IgG, C3 and kappa restricted deposits. Fourteen months post-transplant, he presented with abrupt worsening of graft function, proteinuria and serum IgG kappa monoclonal spike. Allograft biopsy was consistent with recurrent PGNMIGD, considering the native kidney diagnosis and interval post-transplant. He underwent plasmapheresis, IV pooled immune globulin, steroid pulse and taper, and anti-CD-20 Rituximab therapy. Patient had gradual decline in proteinuria and complete resolution of the immune deposits on repeat biopsy 3 months later. Unfortunately he subsequently developed chronic antibody-mediated rejection and transplant glomerulopathy and graft failure 34 months post-transplant.

Conclusions: In a transplant setting, repeat allograft biopsies are frequently performed for graft dysfunction. This provides a good opportunity to study the evolution of the immune deposits following treatment. Our case shows complete histologic resolution of the deposits in allograft PGNMIGD.

15. Effectiveness of mycophenolate mofetil in C3 glomerulonephritis.

Rabasco C, Cavero T, Román E et al.

Kidney Int. 2015 Nov;88(5):1153-60

ABSTRACT

C3 glomerulonephritis is a clinicopathologic entity defined by the presence of isolated or dominant deposits of C3 on immunofluorescence. To explore the effect of immunosuppression on C3 glomerulonephritis, we studied a series of 60 patients in whom a complete registry of treatments was available over a median follow-up of 47 months. Twenty patients had not received immunosuppressive treatments. In the remaining 40 patients, 22 had been treated with corticosteroids plus mycophenolate mofetil while 18 were treated with other immunosuppressive regimens (corticosteroids alone or corticosteroids plus cyclophosphamide). The number of patients developing end-stage renal disease was significantly lower among treated compared with untreated patients (3 vs. 7 patients, respectively). No patient in the corticosteroids plus mycophenolate mofetil group doubled serum creatinine nor developed end-stage renal disease, as compared with 7 (significant) and 3 (not significant), respectively, in patients treated with other immunosuppressive regimens. Renal survival (100, 80, and 72% at 5 years) and the number of patients achieving clinical remission (86, 50, and 25%) were significantly higher in patients treated with corticosteroids plus mycophenolate mofetil as compared with patients treated with other immunosuppressive regimens and untreated patients, respectively. Thus, immunosuppressive treatments, particularly corticosteroids plus mycophenolate mofetil, can be beneficial in C3 glomerulonephritis.

16. Patterns of Clinical Response to Eculizumab in Patients With C3 Glomerulopathy .

Le Quintrec M, Lapeyraque AL, Lionet A et al.

Am J Kidney Dis. 2018 Jul;72(1):84-92. 8

ABSTRACT

Background: Cases reports and small series of patients with C3 glomerulopathy have reported variable efficacy of eculizumab.

Study design: Case series of C3 glomerulopathy.

Setting & participants: Pediatric and adult patients with C3 glomerulopathy treated with eculizumab between 2010 and 2016 were identified through the C3 glomerulopathy French registry database, and a questionnaire was sent to participating French pediatric and adult nephrology centers, as well as one pediatric referral center in Québec, Canada.

Outcomes: Global or partial clinical renal response.

Measurements: Evolution of serum creatinine and proteinuria values.

Results: 26 patients (13 children/adolescents) were included. 22 (85%) patients had received steroids, plasma exchange, or immunosuppressive therapy before eculizumab, and 3 of them had rapid progression of their kidney disease despite treatment. At the initiation of eculizumab therapy, 11 (42%) patients had chronic kidney disease, 7 (27%) had rapidly progressive disease, and 3 (12%) required dialysis. After eculizumab treatment (median duration, 14 months), 6 (23%) patients had a global clinical response; 6 (23%), a partial clinical response; and 14 (54%), no response. Compared with those who had a partial clinical or no response, patients who had a global clinical response had lower estimated glomerular filtration rates, a more rapidly progressive course, and more extracapillary proliferation on kidney biopsy. Age, extent of renal fibrosis, frequency of nephrotic syndrome, low serum C3 and C3 nephritic factor and elevated soluble C5b-9 concentrations, or complement gene variants did not differ between responders and nonresponders.

Limitations: Retrospective design without a control group, relatively small number of cases, inclusion of pediatric and adult cases.

Conclusions: Eculizumab appears to be a potential treatment for patients with crescentic rapidly progressive C3 glomerulopathy. Its benefit in patients with non-rapidly progressing forms seems to be limited.

17. Mycophenolate Mofetil in Combination with Steroids for Treatment of C3 Glomerulopathy A Case Series.

Avasare RS, Canetta PA, Bomback AS et al.

Clin J Am Soc Nephrol 13: 406–413, 2018.

ABSTRACT

Background and objectives: C3 glomerulopathy is a form of complement-mediated GN. Immunosuppressive therapy may be beneficial in the treatment of C3 glomerulopathy. Mycophenolate mofetil is an attractive treatment option given its role in the treatment of other complement-mediated diseases and the results of the Spanish Group for the Study of Glomerular Diseases C3 Study. Here, we study the outcomes of patients with C3 glomerulopathy treated with steroids and mycophenolate mofetil.

Design, setting, participants, & measurements: We conducted a retrospective chart review of patients in the C3 glomerulopathy registry at Columbia University and identified patients treated with mycophenolate mofetil for at least 3 months and follow-up for at least 1 year. We studied

clinical, histologic, and genetic data for the whole group and compared data for those who achieved complete or partial remission (responders) with those who did not achieve remission (nonresponders). We compared remission with mycophenolate mofetil with remission with other immunosuppressive regimens.
Results: We identified 30 patients who met inclusion criteria. Median age was 25 years old (interquartile range, 18-36), median creatinine was 1.07 mg/dl (interquartile range, 0.79-1.69), and median proteinuria was 3200 mg/g creatinine (interquartile range, 1720-6759). The median follow-up time was 32 months (interquartile range, 21-68). Twenty (67%) patients were classified as responders. There were no significant differences in baseline characteristics between responders and nonresponders, although initial proteinuria was lower (median 2468 mg/g creatinine) in responders compared with nonresponders (median 5000 mg/g creatinine) and soluble membrane attack complex levels were higher in responders compared with nonresponders. For those tapered off mycophenolate mofetil, relapse rate was 50%. Genome-wide analysis on complement genes was done, and in 12 patients, we found 18 variants predicted to be damaging. None of these variants were previously reported to be pathogenic. Mycophenolate mofetil with steroids outperformed other immunosuppressive regimens.
Conclusions: Among patients who tolerated mycophenolate mofetil, combination therapy with steroids induced remission in 67% of this cohort. Heavier proteinuria at the start of therapy and lower soluble membrane attack complex levels were associated with treatment resistance.

18. C3 glomerulonephritis secondary to mutations in factors H and I: rapid recurrence in deceased donor kidney transplant effectively treated with eculizumab.
Garg N, Zhang Y, Nicholson-Weller A et al.
Nephrol Dial Transplant (2018) 33: 2260–2265

ABSTRACT
Background: C3 glomerulonephritis (C3GN) is caused by alternate complement pathway over-activation. It frequently progresses to end-stage renal disease, recurs in two-thirds of transplants and in half of these cases progresses to allograft loss. There is currently no proven treatment for C3GN.
Case presentation: We describe a family segregating pathogenic alleles of complement factor H and I (CFH and CFI). The only member carrying both mutations developed C3GN. Prolonged delayed graft function after deceased donor transplantation, heavy proteinuria and isolated C3 hypocomplementemia prompted an allograft biopsy confirming diagnosis of recurrent C3GN.
Discussion: This is the first report of early recurrence of C3GN in an allograft in a patient with known mutations in complement regulatory genes and no preexisting para-proteinemia. Complement activation resulting from ischemia-reperfusion injury from prolonged cold ischemia time unabated in the setting of deficiency of two major complement regulators likely led to the early and severe recurrence. In atypical hemolytic uremic syndrome, the terminal complement cascade activation in the sentinel event initiating endothelial injury; blockade at the level of C5 convertase with eculizumab is uniformly highly effective in management. C3 glomerulopathies (C3GN and dense deposit disease) are a more complex and heterogeneous group. The relative degree of dysregulation at the levels of C3 and C5 convertases and therefore response to eculizumab varies among patients. In our patient, the clinical response to eculizumab was dramatic with recovery of allograft function and complete resolution of proteinuria. We review all

cases of recurrent C3 glomerulopathy treated with eculizumab and discuss how complement biomarkers may aid in predicting response to therapy.

19. C3 glomerulopathy — understanding a rare complement-driven renal disease.
Smith RJH, Appel GB, Blom AM et al.
Nat Rev Nephrol. 2019 Mar;15(3):129-143

ABSTRACT
The C3 glomerulopathies are a group of rare kidney diseases characterized by complement dysregulation occurring in the fluid phase and in the glomerular microenvironment, which results in prominent complement C3 deposition in kidney biopsy samples. The two major subgroups of C3 glomerulopathy - dense deposit disease (DDD) and C3 glomerulonephritis (C3GN) - have overlapping clinical and pathological features suggestive of a disease continuum. Dysregulation of the complement alternative pathway is fundamental to the manifestations of C3 glomerulopathy, although terminal pathway dysregulation is also common. Disease is driven by acquired factors in most patients - namely, autoantibodies that target the C3 or C5 convertases. These autoantibodies drive complement dysregulation by increasing the half-life of these vital but normally short-lived enzymes. Genetic variation in complement-related genes is a less frequent cause. No disease-specific treatments are available, although immunosuppressive agents and terminal complement pathway blockers are helpful in some patients. Unfortunately, no treatment is universally effective or curative. In aggregate, the limited data on renal transplantation point to a high risk of disease recurrence (both DDD and C3GN) in allograft recipients. Clinical trials are underway to test the efficacy of several first-generation drugs that target the alternative complement pathway.

20. Use of Bortezomib in the Treatment of C3 Glomerulonephritis Refractory to Eculizumab and Rituximab.
Hui JW, Banks M, Nadasdy T et al.
Kidney Int Rep (2020) 5, 951–954.

No abstract available

21. Eculizumab in dense- deposit disease after renal transplantation.
Sánchez-Moreno A, De la Cerda F, Cabrera R et al.
Pediatr Nephrol 2014; 29: 2055–2059.

ABSTRACT
Background: Dense-deposit disease (DDD) is a rare glomerulopathy characterized by electron-dense deposits in the glomerular basement membrane. About 50 % of patients with DDD progress to end-stage kidney disease and require dialysis within 10 years of diagnosis, and the disease often recurs after renal transplantation.
Case-diagnosis/treatment: We describe a 14-year-old girl with recurrent DDD in her transplanted kidney. Clinical onset was at 8 years of age, when steroid-resistant nephrotic syndrome was diagnosed with microhematuria, severe hypocomplementemia and normal kidney function.

Although remission was initially observed after several plasma exchanges, nephrotic proteinuria returned and kidney function further declined 1 year later. The patient received a living-related kidney transplant. Initial allograft function was good, but proteinuria reappeared 3 months after transplantation, accompanied by a slight deterioration in kidney function. After histological confirmation of DDD recurrence and subsequent management with plasmapheresis, the patient was treated for 30 months with eculizumab, a humanized monoclonal antibody that binds to C5 complement protein. This intervention proved effective and resulted in complement inhibition, sustained remission of proteinuria and preservation of renal function. A graft biopsy 6 months later showed no progression of the renal lesions.
Conclusions: Early clinical and histological recurrence of DDD in the transplanted kidney in this 14-year-old patient was treated for 30 months with eculizumab. The patient remains asymptomatic, has no proteinuria and her kidney function is intact.

22. Eculizumab as salvage therapy for recurrent monoclonal gammopathy-induced C3 glomerulopathy in a kidney allograft.
Moogi P, Jost PJ, Büttner-Herold M.
BMC Nephrol. 2018 May 3;19(1):106.

ABSTRACT
Background: Monoclonal gammopathy causes several kinds of renal pathology. A rare and special form is monoclonal gammopathy-induced C3 glomerulopathy (MG-C3G). Like idiopathic C3G, MG-C3G frequently leads to end-stage renal disease. MG-C3G frequently recurs after renal transplantation, leading to graft failure in most of the patients. While there is some evidence for successful treatment of recurrent idiopathic C3 glomerulopathy with eculizumab after renal transplantation, nothing is known about its efficacy in the setting of recurrent MG-C3G.
Case presentation: We report a patient with recurrent MG-C3G in a renal allograft that was successfully treated with eculizumab in addition to standard immunosuppression. He had early recurrence of MG-C3G 2 months after transplantation. His graft function successively declined despite high dose steroids and plasmapheresis. Only after therapy with three cycles of bortezomib and continuous therapy with eculizumab, his graft function stabilized. He was still in clinical remission after 28 months of follow-up without having experienced major infectious complications.
Conclusions: Eculizumab may be a safe and effective treatment of recurrent MG-C3G. Because of the high and early recurrence risk, renal transplantation should be reviewed carefully for every individual patient. Subsequent hematopoietic stem cell transplantation may ameliorate long-term renal allograft survival. Eculizumab might serve as a bridging therapy until stem cell transplantation.

23. Practical management of C3 glomerulopathy and immunoglobulin-mediated MPGN: facts and uncertainties.
Fakhouri F, Le Quintrec M, Frémeaux-Bacchi V.
Kidney Int. 2020 Jul 2;S0085-2538(20)30721-3.

ABSTRACT

In recent years, a substantial body of experimental and clinical work has been devoted to C3 glomerulopathy and immunoglobulin-mediated membranoproliferative glomerulonephritis. Despite the rapid accumulation of data, several uncertainties regarding these two rare forms of nephropathies persist. They concern their pathophysiology, classification, clinical course, relevance of biomarkers and of pathology findings and assessment of the efficacy of available therapies. The present review discusses the impact of these uncertainties on the clinical management of patients.

2. RECIDIVA NEFROPATÍA MEMBRANOSA

24. Membranous Nephropathy Posttransplantation: An Update of the Pathophysiology and Management.

Leon J, Pérez-Sáez MJ, Batal I et al.
Transplantation. 2019 Oct;103(10):1990-2002.

ABSTRACT
Membranous nephropathy (MN) is a common cause of nephrotic syndrome after transplantation and is associated with an increased risk of allograft loss. MN may occur either as a recurrent or as a de novo disease. As in native kidneys, the pathophysiology of the MN recurrence is in most cases associated with antiphospholipid A2 receptor antibodies. However, the posttransplant course has some distinct features when compared with primary MN, including a lower chance of spontaneous remission and a greater requirement for adjuvant immunosuppressive therapy to induce complete remission. Although the efficacy of rituximab in primary MN is now well established, no randomized studies have assessed its effectiveness in MN after transplant, and there are no specific recommendations for the management of these patients. This review aims to synthesize and update the pathophysiology of posttransplant MN, as well as to address unsolved issues specific to transplantation, including the prognostic value of antiphospholipid A2 receptor, the risk of living-related donation, the link between de novo MN and rejection, and different therapeutic strategies so far deployed in posttransplant MN. Lastly, we propose a management algorithm for patients with MN who are planning to receive a kidney transplant, including pretransplant considerations, posttransplant monitoring, and the clinical approach after the diagnosis of recurrence.

25. Membranous nephropathy in the kidney allograft.

Filippone EJ, Farber JL.
Clin Transplant. 2016 Nov;30(11):1394-1402.

ABSTRACT
Membranous nephropathy (MN) may occur in a kidney transplant as recurrence of the original disease (rMN) or as a de novo MN (dnMN). rMN often occurs early, within the first year, and often in a mild or subclinical fashion. Recurrence cannot be predicted by clinical features at the time of transplantation. The natural history is increasing proteinuria over time, with less chance for spontaneous remission compared to primary MN (pMN). Antiphospholipase A2 receptor (PLA2R) antibodies should be evaluated in all patients with pMN at the time of transplantation and serially. If titers persist or rise, biopsy is indicated. Irrespective of PLA2R status, any case with proteinuria reaching 1 g/day should be biopsied. No randomized controlled trials have been published regarding treatment of rMN. Observational data support use of rituximab. Given the progressive nature of rMN and lack of spontaneous remissions, a period of observation does not seem justifiable. dnMN occurs with about equal frequency as rMN and shares features of secondary MN in native kidneys. Causes include viral infections (e.g., hepatitis B or C), which should be treated. In some cases, dnMN may represent an atypical alloimmune response. The role of rituximab in dnMN is undefined.

26. Membranous Nephropathy (MN) Recurrence After Renal Transplantation.

Passerini P, Malvica S, Tripodi F et al.

Front Immunol. 2019 Jun 12;10:1326.

ABSTRACT

Primary membranous nephropathy (MN) is a frequent cause of NS in adults. In native kidneys the disease may progress to ESRD in the long term, in some 40-50% of untreated patients. The identification of the pathogenic role of anti-podocyte autoantibodies and the development of new therapeutic options has achieved an amelioration in the prognosis of this disease. MN may also develop in renal allograft as a recurrent or a de novo disease. Since the de novo MN may have some different pathogenetic and morphologic features compared to recurrent MN, in the present paper we will deal only with the recurrent disease. The true incidence of the recurrent form is difficult to assess. This is mainly due to the variable graft biopsy policies in kidney transplantation, among the different transplant centers. Anti-phospholipase A2 receptor (PLA2R) autoantibodies are detected in 70-80% of patients. The knowledge of anti-PLA2R status before transplant is useful in predicting the risk of recurrence. In addition, the serial survey of the anti-PLA2R titers is important to assess the rate of disease progression and the response to treatment. Currently, there are no established guidelines for prevention and treatment of recurrent MN. Symptomatic therapy may help to reduce the signs and symptoms related to the nephrotic syndrome. Anecdotal cases of response to cyclical therapy with steroids and cyclophosphamide have been published. Promising results have been reported with rituximab in both prophylaxis and treatment of recurrence. However, these results are based on observational data, and prospective controlled trials are still missing.

27. Membranous Nephropathy: A Journey From Bench to Bedside.

Francis JM, Beck LH Jr, Salant DJ.

Am J Kidney Dis. 2016 Jul;68(1):138-47.

ABSTRACT

Lessons from an animal model that faithfully resembles human membranous nephropathy (MN) have informed our understanding of the pathogenesis of this organ-specific autoimmune disease and common cause of nephrotic syndrome. After it was established that the subepithelial immune deposits that characterize experimental MN form in situ when circulating antibodies bind to an intrinsic podocyte antigen, it was merely a matter of time before the human antigen was identified. The M-type phospholipase A2 receptor 1 (PLA2R) represents the major target antigen in primary MN, and thrombospondin type 1 domain-containing 7A (THSD7A) was more recently identified as a minor antigen. Serologic tests for anti-PLA2R and kidney biopsy specimen staining for PLA2R show >90% specificity and 70% to 80% sensitivity for the diagnosis of primary MN in most populations. The assays distinguish most cases of primary MN from MN associated with other systemic diseases, and sequential anti-PLA2R titers are useful to monitor treatment response. A positive pretransplantation test result for anti-PLA2R is also helpful for predicting the risk for posttransplantation recurrence. Identification of target epitopes within PLA2R and the genetic association of primary MN with class II major histocompatibility and PLA2R1 variants are 2 additional examples of our evolving understanding of this disease.

28. Prediction of membranous nephropathy recurrence after transplantation by monitoring of anti-PLA2R1 (M-type phospholipase A2 receptor) autoantibodies: a case series of 15 patients.

Seitz-Polski B, Payré C, Ambrosetti D et al.

Nephrol Dial Transplant. 2014 Dec;29(12):2334-42.

ABSTRACT

Background: The predictive value of anti-M-type phospholipase A2 receptor (PLA2R1) autoantibodies for membranous nephropathy (MN) recurrence after renal transplantation remains controversial.

Methods: Our aim was to monitor anti-PLA2R1 IgG4 activity using a sensitive enzyme-linked immunosorbent assay in 15 kidney transplant recipients with MN, and to test the correlation between antibody titres and MN recurrence.

Results: Five patients never exhibited anti-PLA2R1 antibodies, and one of them relapsed. Ten patients (67%) had IgG4 anti-PLA2R1 antibodies at the time of transplantation and during follow-up. The presence of IgG4 anti-PLA2R1 antibodies at the time of kidney transplantation does not imply MN recurrence (P = 0.600, n = 15). However, a positive IgG4 anti-PLA2R1 activity during follow-up (>Month 6) was a significant risk factor for MN relapse (P = 0.0048, n = 10). Indeed, four patients had persistent IgG4 anti-PLA2R1 activity after transplantation and relapsed. Among them, one was successfully treated with rituximab. Another had persistently high IgG4 anti-PLA2R1 activity and exhibited a histological relapse but no proteinuria while on treatment with renin-angiotensin system inhibitors. In contrast, the six other patients who did not relapse exhibited a decrease of their IgG4 anti-PLA2R1 activity following transplant immunosuppression, including two with proteinuria due to biopsy-proven differential diagnoses. A weak transplant immunosuppressive regimen was also a risk factor of MN recurrence (P = 0.0048, n = 10). Indeed, the six patients who received both an induction therapy and a combined treatment with calcineurin inhibitors/mycophenolate exhibited a decrease of IgG4 anti-PLA2R1 activity and did not relapse, while the four patients who did not receive this strong immunosuppressive treatment association had persistently high IgG4 anti-PLA2R1 activity and relapsed.

Conclusion: The monitoring of IgG4 anti-PLA2R1 titres during follow-up helps to predict MN recurrence, and a strong immunosuppressive treatment of anti-PLA2R1 positive patients may prevent recurrence.

29. Pathology of recurrent diseases in kidney allografts: membranous nephropathy and focal segmental glomerulosclerosis.

Kowalewska J.

Curr Opin Organ Transplant. 2013 Jun;18(3):313-8.

ABSTRACT

Purpose of review: Glomerulonephritis is the leading cause of end-stage renal failure in renal transplant recipients. Recurrence of diseases in kidney allograft provides a unique opportunity to study the mechanisms of kidney disorders leading to the underlying native organ failure. There have been new advances in the understanding of the mechanisms of membranous nephropathy and focal segmental glomerulosclerosis (FSGS).

Recent findings: Recent studies of recurrent membranous nephropathy provide evidence of the presence of circulating recipient factor that targets the donor kidney and put forward the evidence

of antiphospholipase A2 receptor antibody pathogenicity in some cases, point to a different pathogenesis of recurrent and de-novo membranous nephropathy, and stress the importance of early morphologic recognition of recurrent membranous nephropathy. New advances in understanding the FSGS include identification of soluble podocyte urokinase receptor as a circulating factor leading to the development and recurrence of FSGS after transplantation, imply that podocyte injury may be a reversible lesion, and suggest a dual role of activated parietal epithelial cells in sclerosing glomerular injury as well as in regeneration and repair.

Summary: Several new mechanisms of glomerular injury have been implicated in the development of recurrent kidney diseases. When further confirmed, some of these might result in early diagnosis and development of better therapy of the respective disorders.

30. Antiphospholipase A2 Receptor Antibody Levels Predict the Risk of Posttransplantation Recurrence of Membranous Nephropathy.

Quintana LF, Blasco M, Seras M et al.

Transplantation. 2015 Aug;99(8):1709-14.

ABSTRACT

Background: Secretory phospholipase A2 receptor (PLA2R) is the target antigen of the auto-antibodies produced in most (~ 70%) patients with primary membranous nephropathy (pMN). The applicability of anti-PLA2R1 antibody monitoring for the prediction of MN recurrence in kidney transplant recipients still is a matter of debate.

Methods: We sought to characterize the presence and concentration of anti-PLA2R antibodies by enzyme-linked immunosorbent assay (ELISA) in a cohort of 21 patients with pMN before and after transplantation to evaluate whether anti-PLA2R concentrations could predict pMN recurrence.

Results: The presence of pMN recurrence was significantly correlated with the existence of a positive ELISA assay at graft biopsy or with high level of anti-PLA2R1 activity before transplantation (P = 0.03). In the receiver operating characteristic analysis, anti-PLA2R levels (cut-off of 45 U/mL) during the pretransplantation period accurately predicted pMN recurrence, with a sensitivity of 85.3%, specificity of 85.1%, negative predictive value of 92%, and an area under the curve of 90.8%. This finding supports the hypothesis that anti-PLA2R cause pMN recurrence in humans and indicates the need to prove in an experimental model. Furthermore, 6 of 7 patients with recurrence were carriers of HLA DQA1* 05:01/05 and DQB1* 02:01, confirming these DQ alleles as those associated with higher anti-PLA2R levels.

Conclusions: This study is the first to demonstrate pretransplantation circulating anti-PLA2R antibodies in a cohort of renal transplant recipients who prospectively developed recurrent disease. Currently, anti-PLA2R levels measured by ELISA may be a rational tool to establish the risk of MN recurrence in renal allograft recipients.

31. Recurrent Membranous Nephropathy After Kidney Transplantation: Treatment and Long-Term Implications.

Grupper A, Cornell LD, Fervenza FC et al.

Transplantation. 2016 Dec;100(12):2710-2716.

ABSTRACT

Background: Membranous nephropathy (MN) can recur in kidney allografts leading to graft dysfunction and failure. The aims of these analyses were to assess MN recurrence, clinical and histologic progression, and response to anti-CD20 therapy.
Methods: Included were 63 kidney allograft recipients with biopsy proven primary MN followed up for 77.0 (39-113) months (median, interquartile range). Disease recurrence was diagnosed by biopsy (protocol or clinical), and follow-up was monitored by laboratory parameters and protocol biopsies.
Results: Thirty of 63 patients (48%) had histologic recurrence often during the first year. In 53% of the cases, recurrence was diagnosed by protocol biopsy. Recurrence risk was higher in patients with higher proteinuria pretransplant [hazard ratio = 1.869 (95% confidence interval, 1.164-3.001) per gram, P = 0.010] and those with anti-phospholipase A2 receptor antibodies [hazard ratio = 3.761 (1.635-8.652), P = 0.002]. Thirteen patients with recurrence had no clinical progression, and in 2, MN resolved histologically. Seventeen of 63 patients (27%) had progressive proteinuria and were treated with anti-CD20 antibodies, resulting in complete response in 9 (53%), partial response in 5 (29%), and no response in 3 (18%). Posttreatment biopsies were obtained in 15 patients and showed histologic resolution in 6 (40%). Disease recurrence did not correlate with graft survival. However, 5 of 11 (45.4%) graft losses were due to recurrent MN. Death-censored graft survival in MN did not differ from that of 273 control recipients with autosomal dominant polycystic kidney disease.
Conclusions: Membranous nephropathy recurs in 48% of cases threatening the allograft. Treatment of early but progressive recurrence with anti-CD20 antibodies is quite effective achieving clinical remission and histologic resolution of MN.

32. The pathology and clinical features of early recurrent membranous glomerulonephritis
Rodriguez EF, Cosio FG, Nasr SH et al.
Am J Transplant 2012 Apr;12(4):1029-38.
ABSTRACT
We assessed the earliest manifestations of recurrent membranous glomerulonephritis (MGN) in renal allografts. Clinical, laboratory and pathologic data were reviewed in 21 patients at the initial biopsy within 4 months post-transplant with evidence of MGN and on follow-up biopsies, compared to a biopsy control group of eight transplants without recurrent MGN. The mean time of first biopsy with pathologic changes was 2.7 months. In each earliest biopsy, immunofluorescence (IF) showed granular glomerular basement membrane (GBM) staining for C4d, IgG, kappa and lambda. IF for C3 was negative or showed trace staining in 16/21. On each MGN biopsy positive by IF, 14/19 showed absence of deposits or rare tiny subepithelial deposits by electron microscopy (EM). At the earliest biopsy, the mean proteinuria was 1.1 g/day; 16 patients had <1 g/day proteinuria. Follow-up was available in all patients (mean 35 months posttransplant). A total of 13 patients developed >1 g/day proteinuria; 12 were treated with: rituximab (n = 8), ACEI and increased prednisone dose (n = 2), ACEI or ARB only (n = 2). All patients showed reduction in proteinuria after treatment. A total of 11/16 patients showed progression of disease by EM on follow-up biopsy. Recognition of early allograft biopsy features aids in diagnosis of recurrent MGN before patients develop significant proteinuria.

33. Recurrent idiopathic membranous nephropathy after kidney transplantation: a surveillance biopsy study.

Dabade TS, Grande JP, Norby SM et al.

Am J Transplant2008 Jun;8(6):1318-22.

ABSTRACT

Membranous nephropathy (MN) is a common cause of nephrotic syndrome in adults. MN can recur after kidney transplantation causing proteinuria, allograft dysfunction and graft failure. In this study we assessed the incidence of MN recurrence utilizing surveillance graft biopsies. The study included 1310 renal allograft recipients from 2000 to 2006. Glomerular diseases were the cause of kidney failure in 28% of patients and 23 (2%) had idiopathic MN. Recurrent MN was diagnosed in eight of 19 patients included in this analysis (42%) 13 +/- 20 months (median = 4; range 2-61 months) after transplant. The initial clinical manifestations of recurrent MN were mild or absent. Urine protein excretion was 825 +/- 959 (64-2286) mg/day and three patients had no proteinuria. Five of seven patients who did not receive additional immunosuppression for MN had significant increases in proteinuria during follow up and three became nephrotic. At diagnosis, light microscopic changes were subtle or absent. All patients had granular glomerular basement membrane deposits of IgG but little or absent C3 by immunofluorescence. Subepithelial deposits were observed in all cases by electron microscopy. In conclusion, idiopathic MN recurred in 42% of patients after transplantation. The initial clinical and histologic manifestations are subtle but the disease is progressive.

MAKERS

34. Neural Epidermal Growth Factor-Like 1 Protein (NELL-1) Associated Membranous Nephropathy

Sethi S, Debiec H, Madden B et al.

Kidney Int . 2020 Jan;97(1):163-174.

ABSTRACT

Membranous nephropathy is characterized by deposition of immune complexes along the glomerular basement membrane. PLA2R and THSD7A are target antigens in 70% and 1-5% of primary membranous nephropathy cases, respectively. In the remaining cases, the target antigen is unknown. Here, laser microdissection of glomeruli followed by mass spectrometry was used to identify novel antigen(s) in PLA2R-negative membranous nephropathy. An initial pilot mass spectrometry study in 35 cases of PLA2R-negative membranous nephropathy showed high spectral counts for neural tissue encoding protein with EGF-like repeats, NELL-1, in six cases. Mass spectrometry failed to detect NELL-1 in 23 PLA2R-associated membranous nephropathy and 88 controls. NELL-1 was localized by immunohistochemistry, which showed bright granular glomerular basement membrane staining for NELL-1 in all six cases. Next, an additional 23 NELL-1 positive cases of membranous nephropathy were identified by immunohistochemistry in a discovery cohort of 91 PLA2R-negative membranous nephropathy cases, 14 were confirmed by mass spectrometry. Thus, 29 of 126 PLA2R-negative cases were positive for NELL-1. PLA2R-associated membranous nephropathy and controls stained negative for NELL-1. We then identified

five NELL-1 positive cases of membranous nephropathy out of 84 PLA2R and THSD7A-negative cases in two validation cohorts from France and Belgium. By confocal microscopy, both IgG and NELL-1 co-localized to the glomerular basement membrane. Western blot analysis showed reactivity to NELL-1 in five available sera, but no reactivity in control sera. Clinical and biopsy findings of NELL-1 positive membranous nephropathy showed features of primary membranous nephropathy. Thus, a subset of membranous nephropathy is associated with accumulation and co-localization of NELL-1 and IgG along the glomerular basement membrane, and with anti-NELL-1 antibodies in the serum. Hence, NELL-1 defines a distinct type of primary membranous nephropathy.

35. Exostosin 1/Exostosin 2-Associated Membranous Nephropathy.
Sethi S, Madden BJ, Debiec H et al.
JAm Soc Nephrol. 2019 Jun;30(6):1123-1136.

ABSTRACT
Background: In membranous nephropathy (MN), which is characterized by deposition of immune complexes along the glomerular basement membrane (GBM), phospholipase A2 receptor (PLA2R) and thrombospondin type 1 domain-containing 7A are target antigens in approximately 70% and 1%-5% of cases of primary MN, respectively. In other cases of primary MN and in secondary MN, the target antigens are unknown.
Methods: We studied 224 cases of biopsy-proven PLA2R-negative MN and 102 controls (including 47 cases of PLA2R-associated MN) in pilot and discovery cohorts. We also evaluated 48 cases of PLA2R-negative presumed primary MN and lupus MN in a validation cohort. We used laser microdissection and mass spectrometry to identify new antigens, which were localized by immunohistochemistry.
Results: Mass spectrometry detected exostosin 1 (EXT1) and exostosin 2 (EXT2) in 21 cases of PLA2R-negative MN, but not in PLA2R-associated MN and control cases. Immunohistochemistry staining revealed bright granular GBM staining for EXT1 and EXT2. Clinical and biopsy findings showed features of autoimmune disease, including lupus, in 80.7% of the 26 EXT1/EXT2-associated MN cases we identified. In the validation cohort, we confirmed that EXT1/EXT2 staining was detected in pure class 5 lupus nephritis (eight of 18 patients) and in presumed primary MN associated with signs of autoimmunity (three of 16 patients); only one of the 14 cases of mixed class 5 and 3/4 lupus nephritis was positive for EXT1/EXT2. Tests in seven patients with EXT1/EXT2-associated MN found no circulating anti-exostosin antibodies.
Conclusions: A subset of MN is associated with accumulation of EXT1 and EXT2 in the GBM. Autoimmune disease is common in this group of patients.

36. Semaphorin 3B-associated Membranous Nephropathy Is a Distinct Type of Disease Predominantly Present in Pediatric Patients.
Sethi S, Debiec H, Madden B et al.
Kidney Int . 2020 Jun 10;S0085-2538(20)30640-2.

ABSTRACT

Membranous nephropathy results from subepithelial antigen-antibody complex deposition along the glomerular basement membrane. Although PLA2R, THSD7A, and NELL-1 account for a majority (about 80%) of the target antigens, the target antigen in the remaining cases is not known. Using laser microdissection of PLA2R-negative glomeruli of patients with membranous nephropathy followed by mass spectrometry we identified a unique protein, Semaphorin 3B, in three cases. Mass spectrometry failed to detect Semaphorin-3B in 23 PLA2R-associated cases of membranous nephropathy and 88 controls. Semaphorin 3B in all three cases was localized to granular deposits along the glomerular basement membrane by immunohistochemistry. Next, an additional eight cases of Semaphorin 3B-associated membranous nephropathy were identified in three validation cohorts by immunofluorescence microscopy. In four of 11 cases, kidney biopsy also showed tubular basement membrane deposits of IgG on frozen sections. Confocal microscopy showed that both IgG and Semaphorin 3B co-localized to the glomerular basement membrane. Western blot analysis of five available sera showed reactivity to reduced Semaphorin 3B in four of four patients with active disease and no reactivity in one patient in clinical remission; there was also no reactivity in control sera. Eight of the 11 cases of Semaphorin 3B-associated membranous nephropathy were pediatric cases. Furthermore, in five cases, the disease started at or below the age of two. Thus, Semaphorin 3B-associated membranous nephropathy appears to be a distinct type of disease; more likely to be present in pediatric patients.

37. A Proposal for a Serology-Based Approach to Membranous Nephropathy.

De Vriese AS, Glassock RJ, Nath KA et al.

J Am Soc Nephrol. 2017 Feb;28(2):421-430.

ABSTRACT

Primary membranous nephropathy (MN) is an autoimmune disease mainly caused by autoantibodies against the recently discovered podocyte antigens: the M-type phospholipase A2 receptor 1 (PLA2R) and thrombospondin type 1 domain-containing 7A (THSD7A). Assays for quantitative assessment of anti-PLA2R antibodies are commercially available, but a semiquantitative test to detect anti-THSD7A antibodies has been only recently developed. The presence or absence of anti-PLA2R and anti-THSD7A antibodies adds important information to clinical and immunopathologic data in discriminating between primary and secondary MN. Levels of anti-PLA2R antibodies and possibly, anti-THSD7A antibodies tightly correlate with disease activity. Low baseline and decreasing anti-PLA2R antibody levels strongly predict spontaneous remission, thus favoring conservative therapy. Conversely, high baseline or increasing anti-PLA2R antibody levels associate with nephrotic syndrome and progressive loss of kidney function, thereby encouraging prompt initiation of immunosuppressive therapy. Serum anti-PLA2R antibody profiles reliably predict response to therapy, and levels at completion of therapy may forecast long-term outcome. Re-emergence of or increase in antibody titers precedes a clinical relapse. Persistence or reappearance of anti-PLA2R antibodies after kidney transplant predicts development of recurrent disease. We propose that an individualized serology-based approach to MN, used to complement and refine the traditional proteinuria-driven approach, will improve the outcome in this disease.

38. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy.

Vweck JR LH, Bonegio RGB, Lambeau G et al.
N Engl J Med 2009;361:11-21

ABSTRACT

Background: Idiopathic membranous nephropathy, a common form of the nephrotic syndrome, is an antibody-mediated autoimmune glomerular disease. Serologic diagnosis has been elusive because the target antigen is unknown.

Methods: We performed Western blotting of protein extracts from normal human glomeruli with serum samples from patients with idiopathic or secondary membranous nephropathy or other proteinuric or autoimmune diseases and from normal controls. We used mass spectrometry to analyze the reactive protein bands and confirmed the identity and location of the target antigen with a monospecific antibody.

Results: Serum samples from 26 of 37 patients (70%) with idiopathic but not secondary membranous nephropathy specifically identified a 185-kD glycoprotein in nonreduced glomerular extract. Mass spectrometry of the reactive protein band detected the M-type phospholipase A(2) receptor (PLA(2)R). Reactive serum specimens recognized recombinant PLA(2)R and bound the same 185-kD glomerular protein as did the monospecific anti-PLA(2)R antibody. Anti-PLA(2)R autoantibodies in serum samples from patients with membranous nephropathy were mainly IgG4, the predominant immunoglobulin subclass in glomerular deposits. PLA(2)R was expressed in podocytes in normal human glomeruli and colocalized with IgG4 in immune deposits in glomeruli of patients with membranous nephropathy. IgG eluted from such deposits in patients with idiopathic membranous nephropathy, but not in those with lupus membranous or IgA nephropathy, recognized PLA(2)R.

Conclusions: A majority of patients with idiopathic membranous nephropathy have antibodies against a conformation-dependent epitope in PLA(2)R. PLA(2)R is present in normal podocytes and in immune deposits in patients with idiopathic membranous nephropathy, indicating that PLA(2)R is a major antigen in this disease.

39. Role of phospholipase A2 receptor 1 antibody level at diagnosis for long-term renal outcome in membranous nephropathy

Mahmud M, O Pinnschmidt H, Reinhard L et al.
PLoS One. 2019 Sep 9;14(9):e0221293.

ABSTRACT

Background: Membranous nephropathy (MN) is an autoimmune disease induced by circulating antibodies against the podocyte protein phospholipase A2 receptor 1 (PLA2R1-ab) in 80% of patients and represents the leading cause of nephrotic syndrome in adults. PLA2R1-ab levels correlate with disease activity and treatment response. However, their predictive role for long-term renal outcome is not clear.

Methods: The aim of this prospective observational multicenter study was to investigate the predictive role of PLA2R1-ab levels at the time of diagnosis for long-term outcome in a cohort of 243 patients with newly diagnosed biopsy-proven PLA2R1-associated MN. Statistical analyses

included Cox proportional hazard models. The primary study endpoint was defined prior to data collection as doubling of serum creatinine or development of end-stage renal disease.
Results: During the median follow-up time of 48 months, 36 (15%) patients reached the study endpoint. Independent predictors for reaching the study endpoint were baseline PLA2R1-ab levels (HR = 1.36, 95%CI 1.11-1.66, p = 0.01), percentage of tubular atrophy and interstitial fibrosis (HR = 1.32, 95%CI 1.03-1.68, p = 0.03), PLA2R1-ab relapse during follow-up (HR = 3.22, 95%CI 1.36-7.60, p = 0.01), and relapse of proteinuria (HR = 2.60, 95%CI 1.17-5.79, p = 0.02). Fifty-four (22%) patients received no immunosuppressive treatment during the study, in 41 (76%) of them PLA2R1-ab spontaneously disappeared during follow-up, 29 (54%) patients had a complete remission of proteinuria, and 19 (35%) had a partial remission. Patients not treated with immunosuppression were more often females and had lower PLA2R1-ab levels, proteinuria, and serum creatinine at baseline compared to patients receiving immunosuppression. However, no conclusion on the efficacy of immunosuppressive therapies can be made, since this was not a randomized controlled study and treatment decisions were not made per-protocol.
Conclusions: PLA2R1-ab levels are, in addition to pre-existing renal damage, predictive factors for long-term outcome and should therefore be considered when deciding the treatment of patients with MN.

40. Thrombospondin type-1 domain-containing 7A in idiopathic membranous nephropathy.
Tomas NM, Beck JR LH, Meyer-Schwesinger C et al.
N Engl J Med 2014;371:2277-87

ABSTRACT
Background: Idiopathic membranous nephropathy is an autoimmune disease. In approximately 70% of patients, it is associated with autoantibodies against the phospholipase A2 receptor 1 (PLA2R1). Antigenic targets in the remaining patients are unknown.
Methods: Using Western blotting, we screened serum samples from patients with idiopathic membranous nephropathy, patients with other glomerular diseases, and healthy controls for antibodies against human native glomerular proteins. We partially purified a putative new antigen, identified this protein by means of mass spectrometry of digested peptides, and validated the results by analysis of recombinant protein expression, immunoprecipitation, and immunohistochemical analysis.
Results: Serum samples from 6 of 44 patients in a European cohort and 9 of 110 patients in a Boston cohort with anti-PLA2R1-negative idiopathic membranous nephropathy recognized a glomerular protein that was 250 kD in size. None of the serum samples from the 74 patients with idiopathic membranous nephropathy who were seropositive for anti-PLA2R1 antibodies, from the 76 patients with other glomerular diseases, and from the 44 healthy controls reacted against this antigen. Although this newly identified antigen is clearly different from PLA2R1, it shares some biochemical features, such as N-glycosylation, membranous location, and reactivity with serum only under nonreducing conditions. Mass spectrometry identified this antigen as thrombospondin type-1 domain-containing 7A (THSD7A). All reactive serum samples recognized recombinant THSD7A and immunoprecipitated THSD7A from glomerular lysates. Moreover, immunohistochemical analyses of biopsy samples from patients revealed localization of THSD7A to podocytes, and IgG eluted from one of these samples was specific for THSD7A.

Conclusions: In our cohort, 15 of 154 patients with idiopathic membranous nephropathy had circulating autoantibodies to THSD7A but not to PLA2R1, a finding that suggests a distinct subgroup of patients with this condition. (Funded by the French National Center for Scientific Research and others.).

SECONDARY MN

41. A Mechanism for Cancer-Associated Membranous Nephropathy.
Hoxha E, Wiech Tm, Stahl PR et al.
N Engl J Med 2016;374:1995-6

No abstract available

IgG SUBCLASSES AND MN

42. Glomerular IgG subclasses in idiopathic and malignancy-associated membranous nephropathy.
Lönnbro-Widgren J, Ebefors K, Mölne J et al.
Clin Kidney J 2015;8:433-9

ABSTRACT
Background: In idiopathic membranous nephropathy (MN), antibodies directed towards the glomerular phospholipase A2 receptor (PLA2R) have mainly been reported to be of IgG4 subclass. However, the role of the different IgG subclasses in the pathogenesis of MN, both in idiopathic MN and in secondary cases, is still unclear. In this retrospective study, we test the hypothesis that the absence of glomerular IgG4 and PLA2R in patients with MN indicates malignant disease.
Methods: The distribution pattern of glomerular IgG subclasses and PLA2R was studied in 69 patients with idiopathic MN and 16 patients with malignancy-associated MN who were followed up for a mean of 83 months.
Results: A significant correlation between the absence of IgG4 and PLA2R and malignancy-associated MN was found. Thus, IgG4 was positive in 45 of 69 patients (65%) with idiopathic MN but only in 5 of 16 patients (31%) with malignancy-associated MN. The other IgG subclasses did not differ statistically between the groups, IgG2-positivity being present in more than 94% of patients in both groups. Thirty-five of 63 patients (56%) with idiopathic MN and 3 of 16 (19%) patients with malignancy-associated MN had glomerular deposits of PLA2R.
Conclusions: We have found that the absence of glomerular IgG4 and PLA2R is common in patients with malignancy-associated MN. In our material, IgG2 could not be used as a marker of underlying malignant disease. Finally, neither IgG1 nor IgG3 seems to be involved in the pathogenesis of MN.

43. Distribution of glomerular IgG subclass deposits in malignancy-associated membranous nephropathy.

Ohtani H, Wakui H, Komatsuda A et al.

Nephrol Dial Transplant 2004;19:574-9

ABSTRACT

Background: Several studies have shown a predominant glomerular deposition of IgG4 in patients with idiopathic membranous nephropathy (MN), whereas significant depositions of other IgG subclasses have been shown in patients with lupus-associated MN and bucillamine-induced MN.

Methods: We examined the distribution patterns of glomerular IgG subclass deposits in 10 patients with malignancy-associated MN (M-MN) and in 15 patients with idiopathic MN by immunofluorescence (IF) microscopy.

Results: The glomerular IF intensities of IgG1 and IgG2 were significantly stronger in the malignancy group than in the idiopathic group ($P<0.05$). In contrast, there were no differences in glomerular IF intensities of IgG3 and IgG4 between the two groups.

Conclusion: Our findings suggest that the distribution patterns of glomerular IgG subclass deposits are different in idiopathic MN and M-MN. The strong IF intensity of glomerular IgG1 and IgG2 in M-MN may provide a possible predictor for this condition.

44. Antigen-Specific IgG subclasses in primary and malignancy associated Membranous Nephropathy.

Von Haxthausen F, Reinhard L, O Pinnschmidt H et al.

Front Immunol. 2018 Dec 20;9:3035.

ABSTRACT

Membranous nephropathy (MN) is an autoimmune disease caused by binding of circulating antibodies to podocyte antigens in the kidney. For decades and still today primary MN has been considered to have an unspecified IgG4-driven autoimmune genesis, while secondary MN has been associated with other diseases, most notably cancer, and not linked to IgG4. Immunologic mechanisms of primary and malignancy-associated MN are assumed to be different, however, this has never been systematically evaluated. The identification of Phospholipase A_2 Receptor 1 (PLA_2R1) and Thrombospondin Type-1 Domain-Containing 7A (THSD7A) as target antigens in MN allows a pathogenesis-driven differential diagnosis. Recent data showing a molecular link between increased THSD7A-expression in tumors and THSD7A-antibody positive MN suggest a similar pathogenesis of malignancy-associated and primary MN. In order to better define the underlying immunologic processes, we systematically analyzed circulating antigen-specific IgG subclasses in the serum of 76 patients with PLA_2R1-associated MN and 41 patients with THSD7A-associated MN in relationship to concurrent malignancy and disease outcome. Twenty-three patients in the study had malignancy-associated MN. We analyzed antigen-specific IgG subclasses in the serum of all patients at baseline and in 55 patients during follow-up by Western blot applying antigens derived from human kidney and lung. At baseline all 117 patients were positive for IgG4-antibodies against either PLA_2R1 or THSD7A, while IgG3, IgG1, and IgG2-antibodies were found in 87, 72, and 26% of patients, respectively. There were no differences in the IgG subclass distribution between patients with primary vs. cancer-associated MN and no association with disease outcome. Moreover, levels

of antigen-specific IgG4-antibodies were not different between primary and malignancy-associated MN and levels of all IgG subclasses did not differ between these groups. Both podocytes and lung bronchioles showed expression of both PLA_2R1 and THSD7A when analyzed by immunofluorescence and Western blot. Every antigen-specific IgG subclass showed identical binding in both organs and autoantibodies bound the respective antigen only under non-reducing conditions. We conclude that antigen-specific IgG subclasses do not differentiate primary from malignancy-associated MN or predict disease prognosis. These data support the view that one common pathway may lead to primary and cancer-associated MN induced by PLA_2R1- or THSD7A-antibodies.

GENETICS

45. Risk HLA-DQA1 and PLA(2)R1 alleles in idiopathic membranous nephropathy.
Stanescu HC, Arcos-Burgos M, Medlar A et al.
N Engl J Med 2011;364: 616-26

ABSTRACT
Background: Idiopathic membranous nephropathy is a major cause of the nephrotic syndrome in adults, but its etiologic basis is not fully understood. We investigated the genetic basis of biopsy-proven cases of idiopathic membranous nephropathy in a white population.
Methods: We performed independent genomewide association studies of single-nucleotide polymorphisms (SNPs) in patients with idiopathic membranous nephropathy from three populations of white ancestry (75 French, 146 Dutch, and 335 British patients). The patients were compared with racially matched control subjects; population stratification and quality controls were carried out according to standard criteria. Associations were calculated by means of a chi-square basic allele test; the threshold for significance was adjusted for multiple comparisons (with the Bonferroni method).
Results: In a joint analysis of data from the 556 patients studied (398 men), we identified significant alleles at two genomic loci associated with idiopathic membranous nephropathy. Chromosome 2q24 contains the gene encoding M-type phospholipase A(2) receptor (PLA(2)R1) (SNP rs4664308, P=8.6×10(-29)), previously shown to be the target of an autoimmune response. Chromosome 6p21 contains the gene encoding HLA complex class II HLA-DQ alpha chain 1 (HLA-DQA1) (SNP rs2187668, P=8.0×10(-93)). The association with HLA-DQA1 was significant in all three populations (P=1.8×10(-9), P=5.6×10(-27), and P=5.2×10(-36) in the French, Dutch, and British groups, respectively). The odds ratio for idiopathic membranous nephropathy with homozygosity for both risk alleles was 78.5 (95% confidence interval, 34.6 to 178.2).
Conclusions: An HLA-DQA1 allele on chromosome 6p21 is most closely associated with idiopathic membranous nephropathy in persons of white ancestry. This allele may facilitate an autoimmune response against targets such as variants of PLA2R1. Our findings suggest a basis for understanding this disease and illuminate how adaptive immunity is regulated by HLA.

46. Epitope Spreading of Autoantibody Response to PLA2R Associates with Poor Prognosis in Membranous Nephropathy.

Seitz-Polski B, Dolla G, Payré C et al.
J Am Soc Nephrol 2016;27:1517-33

ABSTRACT
The phospholipase A2 receptor (PLA2R1) is the major autoantigen in idiopathic membranous nephropathy. However, the value of anti-PLA2R1 antibody titers in predicting patient outcomes is unknown. Here, we screened serum samples from 50 patients positive for PLA2R1 for immunoreactivity against a series of PLA2R1 deletion mutants covering the extracellular domains. We identified reactive epitopes in the cysteine-rich (CysR), C-type lectin domain 1 (CTLD1), and C-type lectin domain 7 (CTLD7) domains and confirmed the reactivity with soluble forms of each domain. We then used ELISAs to stratify 69 patients positive for PLA2R1 by serum reactivity to one or more of these domains: CysR (n=23), CysRC1 (n=14), and CysRC1C7 (n=32). Median ELISA titers measured using the full-length PLA2R1 antigens were not statistically different between subgroups. Patients with anti-CysR-restricted activity were younger (P=0.008), had less nephrotic range proteinuria (P=0.02), and exhibited a higher rate of spontaneous remission (P=0.03) and lower rates of renal failure progression (P=0.002) and ESRD (P=0.01) during follow-up. Overall, 31 of 69 patients had poor renal prognosis (urinary protein/creatinine ratio >4 g/g or eGFR<45 ml/min per 1.73 m(2) at end of follow-up). High anti-PLA2R1 activity and epitope spreading beyond the CysR epitope were independent risk factors of poor renal prognosis in multivariable Cox regression analysis. Epitope spreading during follow-up associated with disease worsening (n=3), whereas reverse spreading from a CysRC1C7 profile back to a CysR profile associated with favorable outcome (n=1). We conclude that analysis of the PLA2R1 epitope profile and spreading is a powerful tool for monitoring disease severity and stratifying patients by renal prognosis.

47. Genetics of membranous nephropathy.
Gupta S, Köttgen A, Hoxha E et al.
Nephrol Dial Transplant. 2018 Sep 1;33(9):1493-1502

ABSTRACT
An HLA-DR3 association with membranous nephropathy (MN) was described in 1979 and additional evidence for a genetic component to MN was suggested in 1984 in reports of familial MN. In 2009, a pathogenic autoantibody was identified against the phospholipase A2 receptor 1 (PLA2R1). Here we discuss the genetic studies that have proven the association of human leucocyte antigen class II and PLA2R1 variants and disease in MN. The common variants in PLA2R1 form a haplotype that is associated with disease incidence. The combination of the variants in both genes significantly increases the risk of disease by 78.5-fold. There are important genetic ethnic differences in MN. Disease outcome is difficult to predict and attempts to correlate the genetic association to outcome have so far not been helpful in a reproducible manner. The role of genetic variants may not only extend beyond the risk of disease development, but can also help us understand the underlying molecular biology of the PLA2R1 and its resultant pathogenicity. The genetic variants identified thus far have an association with disease and could therefore become useful biomarkers to stratify disease risk, as well as possibly identifying novel drug targets in the near future.

MANAGEMENT

48. Treatment of membranous nephropathy: time for a paradigm shift.
Ruggenenti P, Fervenza FC, Remuzzi G.
Nat Rev Nephrol 2017;13:563-7

ABSTRACT
In patients with membranous nephropathy, alkylating agents (cyclophosphamide or chlorambucil) alone or in combination with steroids achieve remission of nephrotic syndrome more effectively than conservative treatment or steroids alone, but can cause myelotoxicity, infections, and cancer. Calcineurin inhibitors can improve proteinuria, but are nephrotoxic. Most patients relapse after treatment withdrawal and can become treatment dependent, which increases the risk of nephrotoxicity. The discovery of nephritogenic autoantibodies against podocyte M-type phospholipase A2 receptor (PLA2R) and thrombospondin type-1 domain- containing protein 7A (THSD7A) antigens provides a clear pathophysiological rationale for interventions that specifically target B-cell lineages to prevent antibody production and subepithelial deposition. The anti-CD20 monoclonal antibody rituximab is safe and achieves remission of proteinuria in approximately two-thirds of patients with membranous nephropathy. In those with PLA2R-related disease, remission can be predicted by anti-PLA2R antibody depletion and relapse by antibody re-emergence into the circulation. Thus, integrated evaluation of serology and proteinuria could guide identification of affected patients and treatment with individually tailored protocols. Nonspecific and toxic immunosuppressive regimens will fall out of use. B-cell modulation by rituximab and second-generation anti-CD20 antibodies (or plasma cell-targeted therapy in anti-CD20 resistant forms of disease) will lead to a novel therapeutic paradigm for patients with membranous nephropathy.

49. Anti-Phospholipase A2 Receptor Antibody Titer Predicts Post-Rituximab Outcome of Membranous Nephropathy.
Ruggenenti P, Debiec H, Ruggiero B et al.
J Am Soc Nephrol 2015;26:2545-58

ABSTRACT

Rituximab induces nephrotic syndrome (NS) remission in two-thirds of patients with primary membranous nephropathy (MN), even after other treatments have failed. To assess the relationships among treatment effect, circulating nephritogenic anti-phospholipase A2 receptor (anti-PLA2R) autoantibodies and genetic polymorphisms predisposing to antibody production we serially monitored 24-hour proteinuria and antibody titer in patients with primary MN and long-lasting NS consenting to rituximab (375 mg/m(2)) therapy and genetic analyses. Over a median (range) follow-up of 30.8 (6.0-145.4) months, 84 of 132 rituximab-treated patients achieved complete or partial NS remission (primary end point), and 25 relapsed after remission. Outcomes of patients with or without detectable anti-PLA2R antibodies at baseline were similar. Among the 81 patients with antibodies, lower anti-PLA2R antibody titer at baseline (P=0.001) and full antibody depletion 6 months post-rituximab (hazard ratio [HR], 7.90; 95% confidence interval [95% CI], 2.54 to 24.60; P<0.001) strongly predicted remission. All 25 complete remissions were preceded by complete anti-PLA2R antibody depletion. On average, 50% anti-PLA2R titer reduction

preceded equivalent proteinuria reduction by 10 months. Re-emergence of circulating antibodies predicted disease relapse (HR, 6.54; 95% CI, 1.57 to 27.40; P=0.01), whereas initial complete remission protected from the event (HR, 6.63; 95% CI, 2.37 to 18.53; P<0.001). Eighteen patients achieved persistent antibody depletion and complete remission and never relapsed. Outcome was independent of PLA2R1 and HLA-DQA1 polymorphisms and of previous immunosuppressive treatment. Therefore, assessing circulating anti-PLA2R autoantibodies and proteinuria may help in monitoring disease activity and guiding personalized rituximab therapy in nephrotic patients with primary MN.

3. RECIDIVA LES

50. Transplant outcomes in kidney recipients with lupus nephritis, and systematic review.

Kim JE, Kim YC, Min SL et al.
Lupus. 2020 Mar;29(3):248-255.

ABSTRACT
Background: Despite improved survival of patients with lupus nephritis (LN), some require kidney transplantation because of progression to end-stage renal disease (ESRD). However, the transplant outcomes of these patients and other recipients have not been thoroughly compared.
Methods: In total, 1848 Korean kidney recipients who underwent transplantation from 1998 to 2017 at two tertiary referral centers were evaluated retrospectively. Among them, 28 recipients with LN, and 50 control recipients matched by age, sex, and donor type, were compared with respect to graft and patient survival. We pooled our data with 17 previous cohort studies in which the graft survival of recipients with LN was described in detail.
Results: During the median follow-up period of 9.5 years (maximum 21 years), graft failure (GF) occurred in 10.7% and 16.0% of LN and control recipients, respectively. No differences were found in the rates of GF and death-censored graft failure or patient survival between the two groups. The risks of acute T cell-mediated and antibody-mediated rejection were also similar between the two groups. The pooled analysis showed similar 1- and 5-year graft survival rates between LN and control recipients.
Conclusions: Kidney transplantation is an acceptable option in patients with concurrent LN and ESRD.

51. Outcome and Prognosis of Patients With Lupus Nephritis Submitted to Renal Transplantation

Albuquerque BC, Salles VB, Tajra RDP et al.
Sci Rep. 2019; 9: 11611.

ABSTRACT
This study aimed to evaluate the epidemiological and clinical profile and outcome of patients with lupus nephritis (LN) submitted to renal transplantation. Retrospective cohort study based on the records of 35 LN patients submitted to renal transplantation at a single center in Brazil between July 1996 and May 2016. The Kaplan-Meier method was used to estimate 6-month, 1-year and 5-year graft survival. The sample included 38 transplantations (3 of which retransplantations). The mean age at the time of SLE diagnosis was 23.7 ± 9.0 years. Most patients were female (94.7%) and 68.4% were non-Caucasian. Twenty-two (57.9%) underwent renal biopsy prior to transplantation. The mean time from SLE diagnosis to transplantation was 10.3 ± 6.4 years. The mean pre-transplantation dialysis time was 3.8 ± 3.7 years. The grafts came from living related (n = 11) or deceased (n = 27) donors. Three (7.9%) patients experienced acute rejection in the first year. Graft and patient survival rates were, respectively, 97.1% and 100% at 6 months, 84.9% and 96.9% at 1 year, and 76.3% and 92.5% at 5 years. One (2.6%) patient had SLE recurrence. Venous thrombosis (p = 0.017) and antiphospholipid syndrome (APS) (p = 0.036) were more prevalent in patients with graft loss. In our cohort of LN patients submitted to renal transplantation, the 5-year survival rate was high, and APS was an important predictor of poor renal outcome (graft loss).

52. Early outcomes in kidney transplant recipients with systemic lupus erythematosus.
López-Morales JM, Quintanilla-González L, Ramírez-Sandoval JC et al.
Rheumatol Int. 2019 Mar;39(3):479-487

ABSTRACT
Kidney transplant (KT) is the best treatment for patients who progress to end-stage renal disease. Short-term outcomes in patients with systemic lupus erythematosus (SLE) following KT are not well known. To describe the postoperative outcomes and complications in SLE patients undergoing KT, we conducted a case-control study from 2010 to 2015 including SLE recipients compared to non-SLE controls matched by age and sex. Demographics, comorbidities, donor characteristics, and preoperative tests were retrieved. Main outcomes were 30-day postoperative allograft function, development of infectious or non-infectious complications, and mortality. 68 patients (34 SLE, 34 non-SLE) were included. SLE recipients had median disease duration of 9 years; SLEDAI-2K of 2, and SLICC/ACR damage index of 3; 16 (47%) were taking prednisone (median dose 5 mg daily) before KT. SLE recipients had a lower frequency of diabetes (0 vs. 27%, p = 0.002). No differences were found in the development of any complication (50% SLE vs. 47% non-SLE, p = 1.00); infectious (44% vs. 41%, p = 1.00), or non-infectious (15% vs. 21%, p = 1.00). There were no deaths in either group, and none of the SLE recipients presented lupus disease activity 30 days after the KT. Allograft function determined by serum creatinine, estimated glomerular filtration rate, delayed graft function, and allograft loss was similar in both groups (p > 0.05). There were no differences between SLE recipients with and without complications. Early postoperative outcomes in SLE patients who undergo KT, including allograft function, development of infectious, non-infectious complications, and mortality, are similar to patients without SLE.

53. Kidney transplantation in systemic lupus erythematosus: Outcomes and prognosis.
Pampa-Saico S, Marcén-Letosa R, Fernández-Rodríguez A et al.
Med Clin (Barc). 2019 Dec 27;153(12):460-463.

ABSTRACT
Introduction: The outcome and prognosis of systemic lupus erythematosus (SLE) in long-term kidney transplantation (KT) is variable. The objective of this study was to analyse the survival of the graft and the patient, comparing rates with a control group (primary glomerulonephritis [PGN]).
Materials and methods: Forty-three patients receiving a KT with diagnosis of lupus nephritis (LN) and 367 patients with PGN were compared between January 1980 and December 2014. The survival causes of loss and death of the graft and the patient were analysed.
Results: There were no significant differences between the variables analysed. The graft survival at five years (80% SLE vs. 70% PGN) and 10 years (63% SLE vs. 55% PGN) and the patient at 5 years (90% SLE vs. 90% PGN) and 10 years (76% LES vs. 79% PGN) were similar. Not recurrence of LN was observed in any patient.
Conclusions: Patients with SLE are similar candidates to KT than that with other immunological kidney diseases. There was no recurrence of the disease in any patient.

54. Renal transplantation in systemic lupus erythematosus: Comparison of graft survival with other causes of end-stage renal disease.

Horta-Baas G, Camargo-Coronel A, Miranda-Hernández DG et al.

Reumatol Clin. 2019 May - Jun;15(3):140-145.

ABSTRACT

Introduction: End-stage renal disease (ESRD) due to lupus nephritis (LN) occurs in 10%-30% of patients. Initially systemic lupus erythematosus (SLE) was a contraindication for kidney transplantation (KT). Today, long-term graft survival remains controversial. Our objective was to compare the survival after KT in patients with SLE or other causes of ESRD.

Methods: All SLE patients who had undergone KT in a retrospective cohort were included. Renal graft survival was compared with that of 50 controls, matched for age, sex, and year of transplantation. Survival was evaluated by the Kaplan-Meier test and the Cox proportional hazards model.

Results: Twenty-five subjects with SLE were included. The estimated 1-year, 2- and 5-year survival rates for patients with SLE were 92%, 66% and 66%. Renal graft survival did not differ between patients with SLE and other causes of ESRD (P=.39). The multivariate analysis showed no significant difference in graft survival between the two groups (hazard ratio, HR=1.95, 95% confidence interval [CI] 0.57-6.61, P=.28). The recurrence rate of LN was 8% and was not associated with graft loss. Acute rejection was the only variable associated with graft loss in patients with SLE (HR=16.5, 95% CI 1.94-140.1, P=.01).

Conclusions: Renal graft survival in SLE patients did not differ from that reported for other causes of ESRD.

55. Long-term survival of kidney grafts in lupus nephritis: a Mexican cohort.

Ramirez-Sandoval JC, Chavez-Chavez H, Wagner M et al.

Lupus. 2018 Jul;27(8):1303-1311.

ABSTRACT

Kidney transplant for patients with lupus nephritis (LN) has satisfactory outcomes in studies with short-term or mid-term follow up. Nevertheless, information about long-term outcomes is scarce. We performed a retrospective matched-pair cohort study in 74 LN recipients compared with 148 non-LN controls matched by age, sex, immunosuppressive treatment, human leukocyte antigen (HLA) matches, and transplant period in order to evaluate long-term outcomes of kidney transplant in LN recipients. Matched pairs were predominantly females (83%), median age at transplant surgery of 32 years (interquartile range 23-38 years), and 66% received a graft from a living related donor. Among LN recipients, 5-, 10-, 15-, and 20-year graft survival was 81%, 79%, 57% and 51%, respectively, and it was similar to that observed in controls (89%, 78%, 64%, and 56%, respectively). Graft loss (27% vs. 21%, p = 0.24) and overall survival (p = 0.15) were not different between LN recipients and controls. Also, there was no difference in episodes of immunological rejection, thrombosis, or infection. Only six LN recipients had biopsy-proven lupus recurrence and three of them had graft loss. In a cohort with a long follow up of kidney transplant recipients, LN recipients had similar long-term graft survival and overall outcomes compared with non-lupus recipients when predictors are matched between groups.

56. Kidney transplantation for end-stage renal disease in lupus nephritis, a very safe procedure: a single Latin American transplant center experience.

Naranjo-Escobar J, Manzi E, Posada JG et al.

Lupus. 2017 Oct;26(11):1157-1165.

ABSTRACT

Background Lupus nephritis (LN) is one of the most frequent complications of SLE and occurs in up to 50% of cases depending on the studied population. Of these, approximately 20% progress to end-stage renal disease (ESRD), with the treatment of choice being a kidney transplant. Objective The objective of this study was to describe the clinical outcome of patients transplanted due to LN, compared with patients transplanted for other causes, in a Latin American population from the Fundación Valle del Lili in Cali, Colombia. Methods Observational, retrospective case study with controls matched by age, sex and type of donor in a single center between 1996 and 2014. Results Sixty-five kidney transplants were performed in patients with LN and ESRD. The survival of patients with LN was 98% at 1, 10 and 15 years (p = .99). For controls by age and sex, survival was also 98% at 15 years post-transplant, and for controls by donor, the survival rate was 100% at 5 years and 98% at 15 years. Graft survival in patients with LN to 1, 5 and 15 years was 92%, 83% and 71%, respectively; for controls by age and sex, it was 90%, 84% and 64%, respectively, and for the controls by donor, it was 89%, 86% and 79%, respectively (p = .7718). There were no statistically significant differences found in the cumulative incidence of acute graft rejection in the first year, but it was found that acute rejection is a factor that relates to the loss of function of the renal graft (p = .032). Of the patients transplanted for LN, two (3.1%) experienced a recurrence of the disease. One patient died after a diagnosis of recurrence of LN due to an infection. Conclusions Kidney transplantation is a good option for patients with ESRD due to LN. In this Hispanic population, the survival of patients, graft survival, and cumulative incidence of graft rejection are not different from those of other transplanted patients. In addition, recurrence of LN was rare, showing the benefits of renal transplantation in LN patients with ESRD.

57. Outcomes in Renal Transplant Recipients With Lupus Nephritis-A Single-Center Experience and Review of the Literature.

Gołębiewska J, Dębska-Ślizień A, Bułło-Piontecka B et al.

Transplant Proc. 2016 Jun;48(5):1489-93.

ABSTRACT

Background: Renal transplantation is the renal replacement therapy of choice in patients with end-stage lupus nephritis (LN). The aim of this study was to evaluate the early and late outcomes of renal transplantation in LN patients in a single transplant center.

Patients and methods: This study analyzed the clinical data of patients who received a renal transplant (RTx) at Gdańsk Transplantation Centre between January 1999 and December 2014.

Results: There were 1296 RTx performed between January 1999 and December 2014, including 21 RTx in 19 LN patients (mean age 40 ± 10 years, 89% female). During the follow-up period (between 1 month and 10.5 years), 1 patient died of urosepsis and 1 of pneumonia. Three RTx recipients with antiphospholipid syndrome lost 5 kidney allografts, including 3 due to acute rejection (AR) during the first posttransplantation month. Kidney allograft survival median was 64 months. Delayed graft function (DGF) and AR were observed in 48% and 33% vs 31% and 21% of LN

patients and other RTx patients, respectively (P = .1 and P = .16 for DGF and AR, respectively). The most common early posttransplantation complications were AR (31%) and perirenal hematomas (29%), and late complications were urinary tract infections (75%). Recurrence of LN in renal allograft was observed in 1 patient and was successfully treated by increasing the basic immunosuppression.
Conclusions: Secondary antiphospholipid syndrome has a major influence on the outcomes of RTx in LN patients. Recurrence of LN has no clinical significance.

58. Renal transplantation in systemic lupus erythematosus: outcome and prognostic factors in 50 cases from a single centre.
Cairoli E, Sanchez-Marcos C, Espinosa G et al.
Biomed Res Int. 2014; 2014:746192.

ABSTRACT
Background: End-stage renal disease (ESRD) is an important cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE).
Objectives: To analyze the outcome and prognostic factors of renal transplantation in patients with ESRD due to SLE from January 1986 to December 2013 in a single center.
Results: Fifty renal transplantations were performed in 40 SLE patients (32 female (80%), mean age at transplantation 36±10.4 years). The most frequent lupus nephropathy was type IV (72.2%). Graft failure occurred in a total of 15 (30%) transplantations and the causes of graft failure were chronic allograft nephropathy (n=12), acute rejection (n=2), and chronic humoral rejection (1). The death-censored graft survival rates were 93.9% at 1 year, 81.5% at 5 years, and 67.6% at the end of study. The presence of deceased donor allograft (P=0.007) and positive anti-HCV antibodies (P=0.001) negatively influence the survival of the renal transplant. The patient survival rate was 91.4% at the end of the study. Recurrence of lupus nephritis in renal allograft was observed in one patient.
Conclusion: Renal transplantation is a good alternative for renal replacement therapy in patients with SLE. In our cohort, the presence of anti-HCV antibodies and the type of donor source were related to the development of graft failure.

59. Outcomes in renal transplant recipients with lupus nephritis: experience at a single center.
Wagner CS, Malafronte P, Demetrio DP et al.
Ren Fail. 2014 Jul;36(6):912-5.

ABSTRACT
Background: The long-term prognosis of renal transplant recipients with systemic lupus erythematosus is still controversial. The outcome of these patients depends on the population studied, race/ethnicity, socioeconomic conditions, donor-related factors and recurrent lupus nephritis (LN), among other factors.
Objective: This study was conducted to evaluate kidney transplantation outcomes for adult Brazilian patients with LN at a single center.

Subjects and method: The archival records of all patients with LN who had received a kidney transplant at Santa Casa of Sao Paulo Hospítal were reviewed. Kaplan-Meier method was used to determine the survival rate.
Results: We identified 18 patients with LN subjected to 22 kidney transplants during the 20-year interval. Two patients received three renal grafts. The majority of the patients were female, with 33.7 ± 10 years at the time of the transplantation, and half of them were African descendants or mixed. Sixteen transplants were performed from deceased donors and six from living-related donors. The patient survival rate was 90%, and graft survival was 68% at 10 years. Chronic allograft nephropathy was the major cause of graft loss. Two patients developed extra-renal manifestations of lupus. There was no clinical or histological evidence of recurrent LN.
Conclusion: Renal transplantation is a method which can provide a long-term survival for patients with SLE and end-stage renal disease.

60. Influence of pretransplantation dialysis time and lupus activity on outcome of kidney transplantation in systemic lupus erythematosus.
Chung MC, Yu TM, Shu KH et al.
Transplant Proc. 2014;46(2):336-8.

ABSTRACT
Background: Kidney transplantation (KT) has better outcome compared with dialysis in lupus patients. The duration lupus patients need to wait before KT remains debatable, especially in patients with lupus activity. We analyzed a renal transplantation database to elucidate if pretransplantation dialysis (PTD) time and lupus activity affected outcome.
Methods: From 1984 to 2012, 31 Chinese lupus nephritis patients underwent KT at our hospital. The lupus activity was defined as nonrenal systemic lupus erythematosus disease activity index (SLE-DAI) score. Biopsy-proven acute rejection/recurrent lupus nephritis (RLN) were recorded. Chronic allograft dysfunction (CAD) was defined as doubling of serum creatinine level. Graft failure was defined as return to dialysis. We calculated relative hazard ratios (HR) with 95% confidence intervals (CI) from Cox proportional-hazards regression models.
Results: In total, 31 lupus patients with KT (7 men and 24 women), with a mean age of 35.3 years at transplantation, were enrolled in this study. The mean follow-up duration was 8.2 years. The mean PTD time was 3.3 years. Both PTD time and lupus activity before transplantation had no effect on CAD and graft failure. Longer PTD time was associated with more acute rejection (HR = 1.20; 95% CI, 1.02-1.41). Also, maximal lupus activity after transplantation was associated with more CAD (HR = 6.44; 95% CI, 1.36-30.57).
Conclusion: For Chinese lupus patients with KT, longer PTD time was associated with worse outcome. Patients should undergo KT immediately if a kidney is available for donation, even with active lupus disease. It is necessary to monitor lupus activity after transplantation due to its effect on outcome.

61. Impact of recurrent lupus nephritis on lupus kidney transplantation: a 20-year single center experience.
Yu TM, Wen MC, Li CY et al.
Clin Rheumatol. 2012 Apr;31(4):705-10.

ABSTRACT

This study was conducted to delineate the frequency of recurrent lupus nephritis in a Chinese kidney transplant cohort and to estimate its impact on long-term transplant outcomes. A total of 32 lupus transplant patients were enrolled in this study, and the medical records were retrospectively reviewed. Patients with unexplained graft abnormalities were subjected to allograft biopsy. Recurrent lupus nephritis was diagnosed by light microscopy, immunofluorescence, and electron microscopy. In addition, to determine the clinical manifestations of recurrent lupus GN in these patients, serum original systemic lupus erythematosus disease activity index (SLEDAI) scores while undergoing allograft biopsy were evaluated. In total, six out of 32 patients (18.8%; mean age, 40.5 ± 9.1 years) were diagnosed as having recurrent lupus nephritis and the mean time at diagnosis was 5.1 ± 4.9 years post-transplantation. According to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 criteria, three of the six cases (50%) were defined as class I, one was class II, one was class IV, and one was class III + V. The graft and patient survival rates of recurrent lupus nephritis (n = 6) were not different from those of patients with other diagnostic entities. Although recurrent lupus nephritis was not uncommon, it did not appear to have a strong negative impact on long-term outcome in Chinese kidney transplant patients. The recurrence was potentially treatable and should not be precluded for receiving transplantation.

62. Recurrence of lupus nephritis after kidney transplantation.

Contreras G, Mattiazzi A, Guerra G et al.

J Am Soc Nephrol. 2010; 21:1200-1207.

ABSTRACT

The frequency and outcome of recurrent lupus nephritis (RLN) among recipients of a kidney allograft vary among single-center reports. From the United Network for Organ Sharing files, we estimated the period prevalence and predictors of RLN in recipients who received a transplant between 1987 and 2006 and assessed the effects of RLN on allograft failure and recipients' survival. Among 6850 recipients of a kidney allograft with systemic lupus erythematosus, 167 recipients had RLN, 1770 experienced rejection, and 4913 control subjects did not experience rejection. The period prevalence of RLN was 2.44%. Non-Hispanic black race, female gender, and age <33 years each independently increased the odds of RLN. Graft failure occurred in 156 (93%) of those with RLN, 1517 (86%) of those with rejection, and 923 (19%) of control subjects without rejection. Although recipients with RLN had a fourfold greater risk for graft failure compared with control subjects without rejection, only 7% of graft failure episodes were attributable to RLN compared and 43% to rejection. During follow-up, 867 (13%) recipients died: 27 (16%) in the RLN group, 313 (18%) in the rejection group, and 527 (11%) in the control group. In summary, severe RLN is uncommon in recipients of a kidney allograft, but black recipients, female recipient, and younger recipients are at increased risk. Although RLN significantly increases the risk for graft failure, it contributes far less than rejection to its overall incidence; therefore, these findings should not keep patients with lupus from seeking a kidney transplant.

63. Risk factors and impact of recurrent lupus nephritis in patients with systemic lupus erythematosus undergoing renal transplantation: data from a single US institution.

Burgos PI, Perkins EL, Pons-Estel GJ et al.
Arthritis Rheum. 2009;60:2757-2766.

ABSTRACT
Objective: To determine the risk factors for recurrent lupus nephritis, allograft loss, and survival among patients with systemic lupus erythematosus (SLE) undergoing kidney transplantation.
Methods: The archival records of all kidney transplant recipients with a prior diagnosis of SLE (according to the American College of Rheumatology criteria) from June 1977 to June 2007 were reviewed. Patients who had died or lost the allograft within 90 days of engraftment were excluded. Time-to-event data were examined by univariable and multivariable Cox proportional hazards regression analyses.
Results: Two hundred twenty of nearly 7,000 renal transplantations were performed in 202 SLE patients during the 30-year interval. Of the 177 patients who met the criteria for study entry, the majority were women (80%) and African American (65%), the mean age was 35.6 years, and the mean disease duration was 11.2 years. Recurrent lupus nephritis was noted in 20 patients (11%), allograft loss in 69 patients (39%), and death in 36 patients (20%). African American ethnicity was found to be associated with a shorter time-to-event for recurrent lupus nephritis (hazard ratio [HR] 4.63, 95% confidence interval [95% CI] 1.29-16.65) and death (HR 2.47, 95% CI 0.91-6.71), although, with the latter, the association was not statistically significant. Recurrent lupus nephritis and chronic rejection of the kidney transplant were found to be risk factors for allograft loss (HR 2.48, 95% CI 1.09-5.60 and HR 2.72, 95% CI 1.55-4.78, respectively). In patients with recurrent lupus nephritis, the lesion in the engrafted kidney was predominantly mesangial, compared with a predominance of proliferative or membranous lesions in the native kidneys.
Conclusion: African American ethnicity was independently associated with recurrent lupus nephritis. Allograft loss was associated with chronic transplant rejection and recurrence of lupus nephritis. Recurrent lupus nephritis is infrequent and relatively benign, without influence on a patient's survival.

64. Recurrent lupus nephritis after transplantation: Clinicopathological evaluation with protocol biopsies.
Çeltİk A, Şen S, Tamer AF et al.
Nephrology (Carlton). 2016 Jul;21(7):601-7.

ABSTRACT
Aim: Lupus nephritis (LN) is an important complication of systemic lupus erythematosus (SLE). The aim is to use indication and protocol biopsies to determine clinicopathological findings and outcomes of patients with LN undergoing kidney transplantation (KTx).
Methods: Patients who underwent KTx due to LN were retrospectively analyzed. Recurrent LN (RLN) was diagnosed by transplant kidney biopsy.
Results: Among 955 KTx patients, 12 patients with LN as the cause of end-stage renal disease were enrolled. Five patients were male. Mean follow-up time was 63 ± 34 months. At the last follow-up visit, mean levels of serum creatinine and proteinuria were 137.0 ± 69.0 μmol/L and 0.26 ± 0.26 g/day, respectively. Eighteen indication and 22 protocol biopsies were performed; 27 biopsies were additionally evaluated by immunofluorescence. In two recipients, subclinical RLN was confirmed by protocol biopsies. Clinical recurrence occurred in four patients. Among patients with

RLN, time from diagnosis of LN to KTx was significantly shorter and use of ATG as induction treatment was significantly lower. Graft loss occurred in two recipients who had clinical RLN. Five-year overall graft survival was 85.7%.

65. Recurrent lupus nephritis after kidney transplantation: a surveillance biopsy study.
Norby GE, Strøm EH, Midtvedt K et al.
Ann Rheum Dis. 2010 Aug;69(8):1484-7.

ABSTRACT
Objectives: To determine the incidence of recurrent lupus nephritis (LN) in renal transplant recipients with systemic lupus erythematosus (SLE).
Methods: All patients with SLE that had undergone transplant with a functioning graft were asked in 2008 to participate in a cross-sectional study. The study included a standardised clinical examination, laboratory tests and a biopsy of the transplanted kidney.
Results: A total of 41 (93%) of a cohort of 44 patients with SLE with renal transplants participated. Of the biopsies, 3 were indication biopsies and 38 were surveillance biopsies. In all, 22 patients (54%) had biopsy-proven recurrence of LN. The majority of the cases were subclinical and characterised as class I/class II LN. Proteinuria (mg protein/mmol creatinine) was significantly increased in patients with recurrence, 70.6 (104.9) mg/mmol versus 11.9 (6.7) mg/mmol in patients without recurrence (p=0.038). Lupus anticoagulant was found more frequently in the patients with recurrence, nine versus two patients (p=0.033). Recurrence of LN was associated with receiving a kidney from a living donor (p=0.049). In all, 83% (34 of 41) had chronic allograft nephropathy in the transplanted kidneys with no difference between patients with recurrence or without.
Conclusions: Subclinical recurrence of LN is common in patients with renal transplants with SLE. The majority of the patients have chronic allograft nephropathy.

66. Recurrent lupus nephritis in renal transplant recipients revisited: it is not rare.
Goral S, Ynares C, Shappell SB et al.
Transplantation. 2003 Mar 15;75(5):651-6.

ABSTRACT
Background: Although recurrent lupus nephritis (RLN) after kidney transplantation is reported to be rare (1%-4%), recent studies suggest a higher incidence. The purpose of this study was to determine the incidence of RLN in a large cohort of renal transplant recipients with systemic lupus erythematosus (SLE).
Methods: The records of 54 renal transplant recipients with SLE were reviewed. Thirty-one patients underwent biopsy because of worsening renal function and proteinuria. All biopsy specimens were evaluated by light microscopy, immunofluorescence (IF), and electron microscopy (EM).
Results: Among the 50 patients with at least 3 months of follow-up, RLN was present in 15 (52% of patients who underwent biopsy, 30% of total patients): mesangial lupus nephritis (LN) (class II) in eight, focal proliferative LN (class III) in four, and membranous LN (class Vb) in three patients. One patient had graft loss because of RLN (class II) at 10.5 years. The duration of dialysis before

transplantation was not different between patients with RLN compared to patients without RLN (P=0.40). Overall patient survival (n=50) was 96% at 1 year and 82% at 5 years, and graft survival was 87% at 1 year and 60% at 5 years. Graft survival was worse in patients who underwent biopsy compared with patients who never underwent biopsy (P<0.01).
Conclusions: RLN is more common than previously reported, but in our series, graft loss because of RLN was rare. Aggressive use of allograft biopsies and morphologic evaluation with IF and EM are important factors in the diagnosis of RLN. The impact of new immunosuppressive agents on the incidence of RLN remains to be seen.

67. The utility of lupus serology in predicting outcomes of renal transplantation in lupus patients: Systematic literature review and analysis of the Toronto lupus cohort.
Yap KS, Urowitz MB, Mahood Q et al.
Semin Arthritis Rheum. 2017 Jun;46(6):791-797.

ABSTRACT
Objectives: To study the utility of lupus serology as a predictor for kidney graft outcome in (a) a systematic literature review (SLR) and (b) the Toronto lupus cohort (TLC).
Methods: For the SLR, a comprehensive literature search was performed to identify the articles reporting on the serology at renal transplantation (RT) and on the outcome of RT. Studies were critically appraised using the Newcastle Ottawa Scale (NOS). Patients who underwent RT in the TLC were identified and grouped into graft failure and graft survival. The serology in both groups was studied.
Results: Of the 749 references, 742 did not have serological status of the patient or were not relevant to the research question. Seven studies in addition to TLC (n = 76) were included in the SLR. The NOS revealed limitations because of small sample size and a short follow-up period. The majority of the grafts survived to at least 1 year regardless of the serology results pre-transplant which is consistent with results of the TLC. Overall, 32 of 1783 patients in the TLC had a RT. In all, 2 patients had a nonfunctional graft, 5 patients had graft failure, and 25 patients had graft survival. Overall, 40% of the graft failures had positive serology compared to 52% in the graft survival, 1 year prior to RT.
Conclusion: The results of this SLR found that the persistence of serological abnormalities at the time of RT was not associated with graft failure. These results are consistent with the results of the TLC.

4. RECIDIVA VASCULITIS Y SD. ANTIFOSFOLÍPIDO

68. Outcome of renal transplantation in patients with pauciimmune small Wessel vasculitis or anti-GBM disease.

Deegens JK, Artz MA, Hottsma AJ et al.
Clin Nephrol. 2003 Jan;59(1):1-9.

ABSTRACT
Aim: Pauci-immune small vessel vasculitis (SVV) and anti-GBM disease are the most common causes of rapidly progressive glomerulonephritis (RPGN) and they frequently lead to end-stage renal disease. For renal replacement therapy, renal transplantation is the preferred treatment option. However, in patients with glomerular diseases, the outcome of renal transplantation can be adversely affected by recurrence of the original disease. The information in the medical literature on the outcome of renal transplantation in patients with RPGN is limited because most data are derived from case studies and from studies involving a small number of patients.
Methods: We studied the outcome of renal transplantation in patients with pauciimmune SVV or anti-GBM disease, transplanted in our center between 1968 and 2000. Patient and graft survival were compared with a matched control group from our hospital. We specifically looked for any evidence of recurrent disease.
Results: Included in the study were 43 patients (31 male, 12 female) with a mean age (+/- SD) of 48 +/- 15 years at transplantation. Patients were diagnosed as Wegener's granulomatosis (n = 8), microscopic polyangiitis (n = 7), renal limited vasculitis (n = 18) and anti-GBM disease (n = 10). The average follow-up was 62 +/- 57 months. No graft was lost due to recurrence of the underlying disease. One patient with Wegener's granulomatosis had a relapse with only extrarenal manifestations 5 months after transplantation. Patient and graft survival at 5 years after transplantation were 77% and 60%. Survival rates were not significantly different from a matched control group of renal transplant patients with other underlying diseases, 79% and 56%, respectively. Patients with pauci-immune SVV or anti-GBM disease developed significantly more malignancies than the control group (p = 0.02).
Conclusions: Recurrence of pauci-immune SVV and anti-GBM disease after transplantation is rare. Renal transplantation can be successfully performed in patients with pauciimmune vasculitis or anti-GBM disease. Physicians should be aware of the greater risk of developing malignancies, especially skin cancer.

69. The long term prognosis of renal transplant in patients with systemic vasculitis.

Moroni G, Torri A, Gallelli B et al.
Am J Transplant. 2007 Sep;7(9):2133-9.

ABSTRACT
Little information is available about the long-term outcome of renal transplantation in patients with systemic vasculitis (SV). We compared the outcomes of 19 renal transplant recipients with SV with those of 38 controls matched for time of transplantation, age, gender and source of donor. The mean post-transplant follow-up was 58 +/- 57 months for vasculitic patients and 61 +/- 49 months for controls. The actuarial 10-year patient survival was 87% in vasculitic patients and 90%

in controls, death-censored graft survival were 84% and 100%, respectively. The risks of acute and chronic rejection, and arterial hypertension were not significantly different between the two groups. Infection was significantly more frequent in vasculitic patients (74% vs. 34%; p = 0.01). Seven patients (36.8%) had a recurrence of vasculitis in mean 45 months after renal transplant (0.076/patients/year). After recurrence, one patient had an irreversible humoral rejection, another died from hemophagocytosis and another restarted dialysis 1 year later. Long-term patient and renal allograft survival in vasculitic patients was good. Although graft function recovered in most relapsers after reinforcement of immunosuppression, one patient died and two lost graft function.

70. Renal transplantation in antineutrophil cytoplasmic antibody-associated vasculitis: a multicenter experience.

Geetha D, Eirin A, True K et al.

Transplantation. 2011 Jun 27;91(12):1370-5.

ABSTRACT

Background: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a common cause of rapidly progressive glomerulonephritis resulting in end-stage renal disease (ESRD). The optimal timing of kidney transplantation (KTX) for ESRD as a result of AAV and the risk of AAV relapse after KTX are not well defined. We report our experience with AAV patients who underwent KTX at our institutions between 1996 and 2010. Median follow-up was 64 months.
Methods: Retrospective multicenter cohort study.
Results: Eighty-five patients (45 men/40 women; mean age 49 years) received a KTX for ESRD secondary to microscopic polyangiitis (n=43) or Wegener's granulomatosis (n=42). Twenty-four patients underwent preemptive KTX and 69 received a living-donor KTX. All patients were in remission at the time of KTX. Fifty-eight patients received induction therapy. In 64 patients, maintenance immunosuppression was with prednisone, mycophenolate mofetil, and tacrolimus. At the time of KTX, 29 patients were ANCA-positive. The vasculitis relapse rate was 0.02 per patient-years and was not influenced by disease category, ANCA subtype, or remission duration before KTX. There were 23 rejection episodes in 13 patients with seven graft losses. Median serum creatinine at 1 year was 1.3 mg/dL in 75 patients with more than 1 year follow-up and 1.4 mg/dL at last follow-up. The graft and patient survival rates were 100% at 1 year, 97.9% and 93.4% at 5 years, and 79.0% and 67.4% at 10 years, respectively.
Conclusions: KTX is a safe and an effective option for treating ESRD secondary to AAV. Relapses are rare with current immunosuppression.

71. Long-term outcome of antineutrophil cytoplasmic antibody-associated small vessel vasculitis after renal transplantation.

Marco H, Mirapeix E, Arcos E et al.

Clin Transplant. May-Jun 2013;27(3):338-47.

ABSTRACT

The survival after renal transplantation of patients with antineutrophil cytoplasmic antibody (ANCA)-associated to systemic vasculitis is as good as in other diseases, although most of the reports are based on small numbers of patients. Furthermore, it is not known whether

comorbidities (cardiovascular [CV] disease and cancer) are more frequent than in general population. We report our experience and the analysis of the published data on this topic. The outcome after transplantation in 49 patients with ANCA-associated small vessel vasculitis was compared with a control group. The relapse rate of vasculitis was 0.01 per patient per year. Comparison with the control patients revealed no difference in long-term outcome, CV mortality or incidence of malignancies. In the published literature, patients with ANCA at transplantation and with Wegener's granulomatosis are at greater risk of relapse. Taking our own results together with the review of the literature, we conclude that patient and graft survival rates compare favorably with those in control group that the recurrence rate is very low and that there is no increase in the incidence of cancer or in CV mortality. Patients with ANCA at transplantation and with Wegener's granulomatosis have a higher relapse rate.

72. Recidiva de vasculitis asociada a anticuerpos anticitoplasma de neutrófilos en un paciente con trasplante renal.

García Cosmes, P, Fraile Gómez, P, Lewczuk K et al.

Nefrología 2016:36(2): 176-180.

ABSTRACT

La afectación renal de las vasculitis asociadas a anticuerpos anticitoplasma de neutrófilos (ANCA) puede conducir a enfermedad renal crónica con necesidad de tratamiento renal sustitutivo. En estos enfermos el trasplante renal ofrece excelentes tasas de supervivencia del injerto y del receptor a largo plazo, por lo que pueden ser trasplantados cuando la enfermedad está en remisión. Sin embargo, la amenaza de recidivas de la enfermedad en el injerto se mantiene, aunque, con las modernas pautas de inmunosupresión, su incidencia es menor. Presentamos el caso de un varón diagnosticado de glomerulonefritis extracapilar tipo III C-ANCA (+) que desarrolló una recidiva de la enfermedad en el injerto renal 8 años después de ser trasplantado. La intensificación de la inmunosupresión con plasmaféresis consiguió controlar la enfermedad.

73. Renal transplantation in systemic vasculitis: when is it safe?

Little MA, Hassan B, Jacques S et al.

Nephrol Dial Transplant. 2009 Oct;24(10):3219-25.

ABSTRACT

Background: There are no clear guidelines on renal transplantation in patients with antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis.

Methods: We undertook a survey of transplant centres across Europe to assess whether there was consensus about how to manage transplantation in patients with vasculitis. We then identified 107 renal allograft recipients whose primary disease was systemic vasculitis and assessed their outcome post-transplant.

Results: All questionnaire respondents felt that vasculitis should be in remission at transplantation, 16% believed that ANCA should be negative pre-transplant and 40% felt that one should wait >12 months after remission before transplanting. Remission was defined by all as an absence of clinical symptoms of vasculitis, but three respondents (13%) also required a negative ANCA test. Overall graft survival was 70% after 10 years (95% C.I. 58-82). A total of 30 (41% of

those with known ANCA status) were ANCA-positive peri-transplantation, while 15 (14%) were transplanted <1 year post-remission. Severe vasculopathy occurred more frequently in ANCA-positive recipients (odds ratio 4.4, 95% C.I. 1.1-16.8, P < 0.05), although causation cannot be determined from this study. Vasculopathy significantly reduced 10-year graft survival to 47% (P < 0.05). However, ANCA status per se was not significantly associated with graft failure. The strongest predictor of death was transplantation <1 year post-vasculitis remission on both univariate and multivariate analysis (hazard ratio 2.3, P < 0.05).
Conclusions: In conclusion, circulating ANCA at transplant was associated with the development of vascular lesions in the graft but was not significantly correlated with graft survival. Most grafts were lost due to patient death, which was more likely if transplantation occurred <12 months following induction of remission of ANCA-positive vasculitis.

74. Recurrent ANCA-associated small vessel vasculitis after transplantation: A pooled analysis.
Nachman PG, Segelmark M, Westman K et al.
Kidney Int. 1999 Oct;56(4):1544-50.

ABSTRACT
Background: Recurrent antineutrophil cytoplasmic antibody (ANCA)-associated small vessel vasculitis (ANCA-SVV) after renal transplantation has been described in case series. However, general information regarding the frequency, character, and predictors of recurrent disease after transplantation is currently lacking. We considered the rate of relapse, whether a positive ANCA at the time of transplantation predicted relapse, and whether cyclosporine A prevented recurrent disease.
Methods: We performed a pooled analysis of published data, added to the experience at the Universities of North Carolina (14 patients) and Lund, Sweden (11 patients). To avoid reporting bias, only case series were included for analysis. Subgroup analysis was performed by disease category (Wegener's granulomatosis, microscopic polyangiitis, or necrotizing crescentic glomerulonephritis) and ANCA staining pattern.
Results: ANCA-SVV recurred in 17.3% of all patients (N = 127), in 20% of cyclosporine A-treated patients (N = 85), and in 25.6% of patients with circulating ANCA at the time of transplantation (N = 39). There was no statistically significant difference in the relapse rate between patients treated and those not treated with cyclosporine A (P = 0.45), between those with and without circulating ANCA at the time of transplant (P = 0.75), or between patients with Wegener's granulomatosis and those with microscopic polyangiitis or necrotizing crescentic glomerulonephritis alone (P = 0.62).
Conclusion: There is a substantial relapse rate in the ANCA-SVV population. Therapy with cyclosporine A does not protect against recurrent ANCA-SVV, and the presence of a positive ANCA at the time of transplantation does not preclude transplantation. These conclusions must be substantiated with a prospective study of renal transplantation in patients with ANCA-SVV so as to optimize their management.

75. Recurrence of ANCA-associated vasculitis following renal transplantation in the modern era of immunosupression.
Gera M, Griffin MD, Specks U et al.
Kidney Int. 2007 Jun;71(12):1296-301.

ABSTRACT

Progressive glomerulonephritis and attendant end-stage renal disease (ESRD) result from antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. The optimum time of kidney transplantation in patients with ESRD due to ANCA-associated vasculitis (AAV) and the risk of renal or nonrenal recurrence of vasculitis after transplantation are unknown. To answer some of these questions, we followed 35 transplant recipients with diagnoses of microscopic polyangiitis (20 patients) and Wegener's granulomatosis (15 patients). The median time from diagnosis to transplantation was 25 months with all patients being in clinical remission. Fifteen patients were ANCA-positive at time of the transplant with 13 preemptive transplants. The most common immunosuppressive strategy included antibody induction, corticosteroid, mycophenolate mofetil, and tacrolimus with acute rejection occurring in eight cases. Overall and death-censored graft survivals were 94 and 100%, respectively, 5 years post-transplantation. Nonrenal relapse occurred in three patients with a satisfactory response to treatment. No clear risk factor to relapse emerged and no detrimental effect to renal function was found. We conclude that transplantation should be considered as the treatment of choice for ESRD due to AAV. Potent antirejection regimes are well tolerated in these patients, are associated with a low risk of recurrence and an absence of AAV-related graft dysfunction.

76. Renal transplantation in antineutrophil cytoplasmic antibody-associated vasculitis.

Moran S, Little MA.

Curr Opin Rheumatol 2014: 26: 37.

ABSTRACT

Purpose of review: This review aims to provide a state-of-the-art perspective on the role of kidney transplantation in cases of end-stage kidney disease due to antineutrophil cytoplasmic antibody (ANCA) vasculitis. We focus on patient and graft survival in recent years, timing of transplant, impact of ANCA status, and relapse of vasculitis in the allograft.

Recent findings: Graft and patient outcome compare very favorably with other causes of kidney failure and several recent studies have indicated that these outcomes have improved further in recent years. Relapse of vasculitis posttransplant appears to be lower in the modern era of transplant induction. There may be an excess mortality in those transplanted less than 1 year after induction of vasculitis remission, so it is probably wise to wait for this period before proceeding with the graft. ANCA status at transplant does not appear to influence outcome.

Summary: Kidney transplantation is an excellent treatment for kidney failure due to vasculitis, although one must never lose sight of the cause of the original vasculitic kidney failure in the event of clinical deterioration of an allograft recipient, even if the diagnosis of ANCA vasculitis was many years previously.

77. Successful induction of remission with rituximab for relapse of ANCA-associated vasculitis post-kidney transplant: report of two cases.

Geeta D, Seo P, Specks U et al.

Am J Transplant. 2007 Dec;7(12):2821-5.

ABSTRACT

Kidney transplantation should be considered the treatment of choice for patients with end-stage renal disease due to antineutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV). However, relapses of AAV have been reported to occur in 9-40% of cases following kidney transplantation and may adversely affect allograft outcome. These relapses are usually treated with cyclophosphamide (CYC) and glucocorticoids, but the repeated use of CYC carries a risk of substantial toxicity that may limit or prohibit its use in some patients. B lymphocytes have been implicated in the pathogenesis of AAV, and their depletion has been effective as salvage therapy for refractory disease in the nontransplant setting. We report the successful induction of remission using rituximab in two patients who suffered relapse of AAV post-kidney transplant. Given the substantial morbidity and adverse effects of CYC, rituximab appears to be a suitable alternative agent to treat relapses of AAV posttransplantation.

78. Rituximab for remission induction in recurrent ANCA-associated glomerulonephritis postkidney transplant.
Murakami C, Manoharan P, Carter-Monroe N et al.
Transpl Int. 2013 Dec;26(12):1225-31.

ABSTRACT
Kidney transplantation (KTX) is the treatment of choice for patients with end-stage renal disease (ESRD) due to ANCA-associated vasculitis (AAV). Recurrent ANCA-associated glomerulonephritis (GN) occurs after KTX and may adversely affect allograft survival. Cyclophosphamide (CYC) combined with glucocorticoids has been the cornerstone of treatment for recurrent GN. Rituximab (RTX), a B-cell-depleting monoclonal antibody, is approved for remission induction in AAV. We report the clinical presentation and outcomes of five KTX recipients treated with RTX for biopsy-confirmed recurrent GN. The median age at the time of KTX was 26 years (four Caucasian, three females). All patients were in remission with four being ANCA positive at time of KTX. Recurrent GN occurred at a median of 26 months post-KTX. All relapses were treated with RTX and glucocorticoids. Four patients achieved disease remission; the fifth patient was refractory to treatment with RTX and CYC. Follow-up biopsies (n = 3) showed resolution of active GN in two patients and persistent active GN in one patient. RTX is an alternative to CYC for remission induction in recurrent AAV-associated GN in KTX patients.

79. Outcome of Kidney Transplant in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis.
Buttigieg J, Henderson L, Kidder D.
Exp Clin Transplant. 2017 Oct;15(5):509-515.

ABSTRACT
Objectives: Kidney transplant outcomes in patients with antineutrophil cytoplasmic antibody-associated vasculitis are comparable with outcomes in patients transplanted for other causes. Here, we report our single center experience of kidney transplant in patients with this condition and a pooled analysis of published studies.
Materials and methods: This retrospective study included all patients with end-stage kidney disease secondary to antineutrophil cytoplasmic antibody-associated vasculitis who received a kidney transplant between 1987 and 2013 in the East of Scotland. We examined patient and graft

survival and disease recurrence after transplant. We also performed a pooled analysis of published literature.
Results: We identified 24 patients who received a total of 31 kidney allografts. Median age at first transplant was 45.5 years (range, 18-68 y), and median follow-up after transplant was 60 months (range, 0.5-226 mo). All patients were positive for antineutrophil cytoplasmic antibody (71% by proteinase 3 and 29% by myeloperoxidase) at diagnosis. Patient survival at 1 and 5 years was 92% and 88%, with corresponding death-censored allograft survival of 93% and 71%. Overall patient and allograft relapse rates were 0.022 and 0.016 relapse/patient-years. The pooled analysis comprised 20 studies (1169 patients). Patient/graft survival ranged from 64% to 80%/77% to 100% at 5 years and from 60% to 100%/59% to 84% at 10 years. Relapse rate was significantly higher in patients with positive antineutrophil cytoplasmic antibody at transplant (14% vs 5%; P = .042).
Conclusions: Our experience shows that kidney transplant remains a safe option for patients with end-stage kidney disease secondary to antineutrophil cytoplasmic antibody-associated vasculitis. Disease relapse posttransplant is uncommon and associated with pretransplant relapse. Pooled analyses suggest that relapse rate is higher in patients with positive antineutrophil cytoplasmic antibody at transplant. Multicenter registry data are needed to define renal outcome predictors in antineutrophil cytoplasmic antibody-associated vasculitis.

80. Recurrence from primary and secondary glomerulopathy after renal transplant.
Canaud G, Audard V, Kofman T et al.
Transpl Int. 2012. Aug;25(8):812-24

ABSTRACT
Glomerulonephritis is the primary cause of end-stage renal failure in 30-50% of kidney transplant recipients and recurrence of the initial disease is an important determinant of long-term graft outcome after transplantation. Although renal transplantation remains the best treatment option for patients with end stage renal diseases in most cases, diagnosis and management of recurrences of glomerulopathies are critical for the optimization and improvement of long-term kidney transplant graft survival and provide a unique opportunity to explore the pathogenesis of native kidney disease. This review aims to update knowledge for a large panel of recurrent primary and secondary glomerulonephritis after kidney transplantation, excluding diabetic nephropathy including primary focal and segmental glomerulosclerosis, membranous nephropathy, IgA nephropathy, membranoproliferative glomerulonephritis, lupus, vasculitis but also less usual secondary nephropathy related to sarcoidosis, AA and AL amyloidosis, monoclonal immunoglobulin deposition disease, and fibrillary glomerulonephritis.

81. Renal Transplantation in Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis.
Hruskova Z, Geetha D, Tesar V.
Nephrol Dial Transplant 2015 Apr;30 Suppl 1:i159-63.

ABSTRACT
Despite major advances in the management of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) achieved in the last decades, a large proportion of AAV patients still develop end-stage renal disease. The survival of AAV patients dependent on dialysis is significantly

worse compared with dialysis-independent AAV patients, but is comparable to other non-diabetic patients requiring dialysis. Renal transplantation (RTx) is the method of choice among renal replacement therapies and there has been increasing evidence that it is a suitable method with favorable patient- and graft-survival also in AAV patients. It is recommended to perform RTx after ≥12 months of remission, and ANCA positivity at the time of RTx is generally not considered a contraindication. Even though the risk of relapse after RTx is relatively low with current post-transplant immunosuppressive regimens, disease recurrence may occur. Besides cyclophosphamide, rituximab might become a therapeutic alternative for post-transplant AAV recurrence in the near future but its efficacy and safety in this setting needs to be confirmed in larger studies.

HISTORIA NATURAL DE LA EVOLUCIÓN DEL INJERTO EN LOS PACIENTES CON ANTICUERPOS ANTICARDIOLIPINA (ACAS).

ACAs IgG o IgM.
AL; anticoagulante lúpico
Síndrome antifosfolípido (revisar definición: tener un evento trombótico u obstétrico y presentar 2 test positivos en 2 determinaciones separadas 3 meses)
Anticuerpos IgA anti β2-glicoproteína I (ver los tres últimos artículos del grupo Hospital 12 de octubre):

82. Anticardiolipin antibodies and 12-month graft function in kidney transplant recipients: a prognosis cohort survey.
Gauthier M, Canoui-Poitrine F, Guéry E et al.
Nephrol Dial Transplant 2018 Apr 1;33(4):709-716.

ABSTRACT
Background: In kidney transplant recipients, anticardiolipin (ACL) antibodies without antiphospholipid syndrome (APS) are found in up to 38% of patients and could be associated with thrombotic events (TEs). However, the prognostic role of ACL regarding kidney transplant and patient's outcomes have still not been well defined.
Methods: We conducted an observational, monocentric, retrospective cohort study including 446 kidney transplant recipients and standardized follow-up: 36-month allograft and patient survival, 12-month estimated glomerular filtration rate (eGFR) and 3- and 12-month screening biopsies.
Results: ACL tests were run on 247 patients, 101 were positive (ACL+ group, 41%) and 146 were negative (ACL- group, 59%). Allografts and patient survival within 36 months as TE were similar between both groups [hazard ratio (HR) = 1.18 and HR = 0.98, respectively]. The 12-month eGFR was significantly lower in the ACL+ group [median (95% confidence interval) 48.5 (35.1-60.3) versus 51.9 (39.1-65.0) mL/min/1.73 m2, P= 0.042]. ACL+ was independently associated with eGFR decrease (P = 0.04). In 12-month screening biopsies, tubular atrophy was significantly more severe in the ACL+ group compared with the ACL- group (P = 0.02).
Conclusions: ACL without APS before kidney transplantation is an independent risk factor of eGFR decline within the first-year post-transplant without over-incidence of TEs. Specific

immunosuppressive therapy including mammalian target of rapamycin inhibitors should be discussed in the future.

83. Ten-year renal allograft survival of patients with antiphospholipid antibody syndrome.
Vaidya S.
Clin Transplant. 2012 Nov-Dec;26(6):853-6.

ABSTRACT
Background: Long-term allograft survival of antiphospholipid antibody syndrome (APAS) patients as well as patients who have antiphospholipid antibodies but no thrombotic complications remains largely unknown. This study evaluates long-term allograft survival of APA as well as patients with APAS.
Methods: During the study period from January 1, 1992 through May 31, 2009, 1625 patients with ESRD awaiting renal transplants were screened for APAS. Ninety-four (5.8%) of these patients had circulating levels of anticardiolipin antibodies (ACA) and 39 of these patients had documented evidence of clotting disorders and were diagnosed with APAS. Twenty-one patients with APAS received transplants on either low molecular weight (LMW) heparin or Coumadin as anticoagulation therapy. Of 94 patients with only ACA, 46 received renal transplants. Of the remaining 1492 patients, 1285 patients with no evidence of either ACA or APAS received renal transplants.
Results: Ten-yr allograft survival of patients with APAS treated with Coumadin was similar to those treated with LMW heparin (18% vs. 20%, NS). However, those allograft survivals were significantly lower than those patients positive for ACA (28%) alone (ACA vs. LMW heparin or Coumadin p=0.0001).
Conclusion: Despite anticoagulation therapies, patients with APAS have lower long-term graft survival than those patients who have circulating ACA but no APAS.

84. Severe vascular lesions and poor functional outcome in kidney transplant recipients with lupus anticoagulant antibodies
Canaud G, Bienaimé F, Noël LH et al.
Am J Transplant 2010 Sep;10(9):2051-60.

ABSTRACT
The impact of antiphospholipid antibodies (APA) on clinical outcome and graft histology following renal transplantation remains poorly known and controversial. We retrospectively explored the functional and histological significance of APA, primarily lupus anticoagulant (LA), in kidney transplant recipients using a systematic evaluation of 3- and 12-month posttransplant screening biopsies and glomerular filtration rate measurements (mGFR). During the study period, 37 patients had APA (2.7%), primarily LA, and 12 fulfilled antiphospholipid syndrome (APS) diagnostic criteria (0.8%) at the time of transplantation. Early after transplantation, 4 of the 12 APS patients died. Early thrombosis of graft vessels and deep venous thrombosis occurred more frequently in APA+ patients than in controls (27% vs. 7%, $p < 0.05$ and 35% vs. 14%, $p < 0.05$, respectively). The survival rate was significantly lower in patients with APS. Strikingly, the hallmark lesions of APS-associated nephropathy (APSN) were found in most of screening graft biopsies in APA+ patients

but not in the controls. Accordingly, APA+ patients had a dramatic increase in chronic vascular scores and a faster decline in mGFR at 1 year. In conclusion, renal transplantation may be life-threatening in APS patients, and the presence of LA at the time of transplantation is associated with a high rate of allograft APSN and poor transplantation outcomes.

85. Significance of anticardiolipin antibodies on short and long-term allograft survival and function following kidney transplantation.

Forman JP, Lin J, Pascual M et al.

Am J Transplant. 2004 Nov;4(11):1786-91.

ABSTRACT

The significance of anticardiolipin antibodies (ACAs) prior to renal transplantation is unclear. We studied a cohort of 337 patients who underwent renal transplantation from 1996 to 2001. Follow-up continued until allograft loss, patient death or 31 December 2002. The primary outcome was a composite endpoint of death-censored allograft loss or a 25% reduction in estimated glomerular filtration rate (GFR) from 1-month post-transplant. Secondary outcomes were allograft loss, a 25% reduction in GFR, acute rejection and creatinine at 1 year. IgG and IgM ACA titers were positive (> or =15) in 18.1% of recipients. There were no significant differences at baseline between recipients, except coumadin therapy in those with positive ACA titers (20% vs. 7.4%). Post-transplant, there was no increase in the primary outcome in ACA-positive patients, even after adjustment for anticoagulation with coumadin (HR = 1.42 [0.68, 2.96]). There was no difference in secondary outcomes between those with or without positive titers. Two of five patients with very high titers (>50) who were not anticoagulated had early graft loss. A positive ACA titer prior to kidney transplantation was not associated with inferior renal outcomes after transplantation, although more research is required to address the prognostic significance of very high ACA titers.

86. Antiphospholipid Syndrome and Renal Allograft Thrombosis.

Morales JM, Serrano M, Martinez-Flores JA et al.

Transplantation 2019 Mar;103(3):481-486.

ABSTRACT

Renal allograft thrombosis is the most frequent and devastating complication in the early postrenal transplantation period. Several risk factors to develop graft thrombosis depending on donors and recipients are well known. Antiphospholipid syndrome (APS) is well recognized as an important cause of kidney injury, with specific clinical and histological features that may lead to renal injury caused by thrombosis at any location within the renal vasculature. There are 3 forms of APS, primary (the most common form), associated to other systemic autoimmune diseases (SAD-APS), and catastrophic. Nevertheless, patients with SAD-APS and renal failure only represent 2% to 5% in hemodialysis or transplantation. The presence of pretransplant antiphospholipid antibodies increases risk of graft thrombosis. A new form of APS based on IgA anti-β-2-glycoprotein-I (B2GPI) antibodies, representing up to 30% of patients in end-stage renal disease and renal transplantation, is the main independent risk factor for graft thrombosis and early graft loss after renal transplantation. In addition, B2GP1 bound to IgA aB2GP1 immunocomplexes have been described as a marker to predict thrombosis after renal transplantation in patients with

antiphospholipid antibodies. Anticoagulation remains the main treatment to prevent renal allograft thrombosis, although new preventive strategies are coming. Future studies may help to identify better therapeutic targets.

OPCIONES TERAPÉUTICAS

Anticoagulación. A todos (ACAS IgG/IgM, AL, SAFL, ACAs IgA) o solo a algunos (SAFL).
Sirolimus/everolimus como inmunosupresor de elección en la pauta de mantenimiento.
Eculizumab en las crisis (MAT).

87. Frequency, potential risk and therapeutic intervention in end-stage renal disease patients with antiphospholipid antibody syndrome: a multicenter study.
Vaidya S, Sellers R, Kimball P et al.
Transplantation 2000 Apr 15;69(7):1348-52.

ABSTRACT
Background: Antiphospholipid antibody syndrome (APAS) is characterized by the presence of anticardiolipin antibodies (ACA) in association with thrombotic disorders of arterial and/or venus systems, spontaneous abortion(s) or thrombocytopenia.
Methods: In this multicenter study, 502 end-stage renal disease (ESRD) patients awaiting renal transplants were screened to determine the frequency of APAS, the potential risk associated with APAS, and strategies for therapeutic intervention. Ninety-three patients (19%) had high titers of ACA. Twenty-three patients had documented evidence of one or more of the thrombotic disorders such as lupus, frequent abortions, frequent thrombosis of arteriovenous shunts, biopsy-proven microrenal angiopathy, or thrombocytopenia and thus were diagnosed with APAS. Of these 23 patients, 11 received kidney transplants either with (4 patients) or without (7 patients), concomitant anticoagulation therapy.
Results: All seven of the patients with APAS not treated with anticoagulation therapy lost their allografts within 1 week as a result of renal thrombosis. In contrast, three out of four transplant patients with APAS treated with anticoagulation therapy maintained their allografts for over 2 years. The fourth patient lost his graft within a week because of thrombosis. Of the remaining 70 patients with high titers of ACA but no evidence of thrombotic disorders, 37 received kidney transplants. None lost their allografts as a result of thrombosis. Our data suggest that, although 19% of our ESRD patients exhibit high titer of ACA, only 5% of the patients have APAS.
Conclusion: In conclusion, our data suggest that the patients with APAS are at high risk of posttransplant renal thrombosis. Anticoagulation therapy could prevent patients from posttransplant thrombosis in patients with APAS.

88. Inhibition of the mTORC pathway in the antiphospholipid syndrome.
Canaud G, Bienaimé F, Tabarin F et al.
N Engl J Med 2014 Jul 24;371(4):303-12.

ABSTRACT

Background: Although thrombosis is considered the cardinal feature of the antiphospholipid syndrome, chronic vascular lesions are common, particularly in patients with life-threatening complications. In patients who require transplantation, vascular lesions often recur. The molecular pathways involved in the vasculopathy of the antiphospholipid syndrome are unknown, and adequate therapies are lacking.
Methods: We used double immunostaining to evaluate pathway activation in the mammalian target of rapamycin complex (mTORC) and the nature of cell proliferation in the vessels of patients with primary or secondary antiphospholipid syndrome nephropathy. We also evaluated autopsy specimens from persons who had catastrophic antiphospholipid syndrome. The molecular pathways through which antiphospholipid antibodies modulate the mTORC pathway were evaluated in vitro, and potential pharmacologic inhibitors were also tested in vitro. Finally, we studied the effect of sirolimus in kidney-transplant recipients with the antiphospholipid syndrome.
Results: The vascular endothelium of proliferating intrarenal vessels from patients with antiphospholipid syndrome nephropathy showed indications of activation of the mTORC pathway. In cultured vascular endothelial cells, IgG antibodies from patients with the antiphospholipid syndrome stimulated mTORC through the phosphatidylinositol 3-kinase (PI3K)-AKT pathway. Patients with antiphospholipid syndrome nephropathy who required transplantation and were receiving sirolimus had no recurrence of vascular lesions and had decreased vascular proliferation on biopsy as compared with patients with antiphospholipid antibodies who were not receiving sirolimus. Among 10 patients treated with sirolimus, 7 (70%) had a functioning renal allograft 144 month after transplantation versus 3 of 27 untreated patients (11%). Activation of mTORC was also found in the vessels of autopsy specimens from patients with catastrophic antiphospholipid syndrome.
Conclusions: Our results suggest that the mTORC pathway is involved in the vascular lesions associated with the antiphospholipid syndrome.

89. Eculizumab prevents recurrent antiphospholipid antibody syndrome and enables successful renal transplantation.

Lonze BE, Zachary AA, Magro CM et al.

Am J Transplant 2014 Feb;14(2):459-65.

ABSTRACT

Renal transplantation in patients with antiphospholipid antibodies has historically proven challenging due to increased risk for thrombosis and allograft failure. This is especially true for patients with antiphospholipid antibody syndrome (APS) and its rare subtype, the catastrophic antiphospholipid antibody syndrome (CAPS). Since a critical mechanism of thrombosis in APS/CAPS is one mediated by complement activation, we hypothesized that preemptive treatment with the terminal complement inhibitor, eculizumab, would reduce the extent of vascular injury and thrombosis, enabling renal transplantation for patients in whom it would otherwise be contraindicated. Three patients with APS, two with a history of CAPS, were treated with continuous systemic anticoagulation together with eculizumab prior to and following live donor renal transplantation. Two patients were also sensitized to human leukocyte antigens (HLA) and required plasmapheresis for reduction of donor-specific antibodies. After follow-up ranging from 4 months to 4 years, all patients have functioning renal allografts. No systemic thrombotic events or early graft losses were observed. While the appropriate duration of treatment remains to be

determined, this case series suggests that complement inhibitors such as eculizumab may prove to be effective in preventing the recurrence of APS after renal transplantation.

90. Eculizumab improves posttransplant thrombotic microangiopathy due to antiphospholipid syndrome recurrence but fails to prevent chronic vascular changes.
Canaud G, Kamar N, Anglicheau D et al.
Am J Transplant 2013 Aug;13(8):2179-85.

ABSTRACT
Thrombotic microangiopathy (TMA) is one of the hallmark vascular lesions of antiphospholipid syndrome nephropathy (APSN). These lesions are at high risk of recurrence after kidney transplantation. The complement pathway is thought to be active in this process. We used eculizumab to treat three consecutive kidney transplant recipients with posttransplant TMA due to APSN recurrence that was resistant to plasmapheresis and explored the complement deposition and apoptotic and vascular cell markers on the sequential transplant biopsies. Treatment with eculizumab resulted in a rapid and dramatic improvement of the graft function in all three patients and in improvement of the TMA lesions within the graft. None of these patients had TMA flares after eculizumab was withdrawn. At the time of TMA diagnosis, immunofluorescence studies revealed intense C5b-9 and C4d depositions at the endothelial cell surface of the injured vessels. Moreover, C5b-9 colocalized with vessels exhibiting a high rate of apoptotic cells. Examination of sequential biopsies during eculizumab therapy showed that TMA lesions, C4d and apoptotic markers were rapidly cleared but the C5b-9 deposits persisted for several months as a footprint of the TMA. Finally, we noticed that complement inhibition did not prevent the development of the chronic vascular changes associated with APSN. Eculizumab seems to be an efficient method for treating severe forms of posttransplant TMA due to APSN recurrence. Terminal complement inhibition does not prevent the development of chronic APSN.

REVISIONES SOBRE EL TEMA

91. Antiphospholipid syndrome and kidney disease
Bienaimé F, Legendre C, Terzi F et al.
Kidney Int 2017 Jan;91(1):34-44.

ABSTRACT
The antiphospholipid syndrome is a common autoimmune disease caused by pathogenic antiphospholipid antibodies, leading to recurrent thrombosis and/or obstetrical complications. Importantly for nephrologists, antiphospholipid antibodies are associated with various renal manifestations including large renal vessel thrombosis, renal artery stenosis, and a constellation of intrarenal lesions that has been termed antiphospholipid nephropathy. This last condition associates various degrees of acute thrombotic microangiopathy, proliferative and fibrotic lesions of the intrarenal vessels, and ischemic modifications of the renal parenchyma. The course of the disease can range from indolent nephropathy to devastating acute renal failure. The pejorative impact of antiphospholipid antibody-related renal complication is well established in the context

of systemic lupus erythematous or after renal transplantation. In contrast, the exact significance of isolated antiphospholipid nephropathy remains uncertain. The evidence to guide management of the renal complications of antiphospholipid syndrome is limited. However, the recent recognition of the heterogeneous molecular mechanisms underlying the progression of intrarenal vascular lesions in antiphospholipid syndrome have opened promising tracks for patient monitoring and targeted therapeutic intervention.

92. The emerging role of complement inhibitors in transplantation

Frémeaux-Bacchi V, Legendre C.

Kidney Int 2015 Nov;88(5):967-73.

ABSTRACT

The role of complement in the biology of kidney transplantation is becoming more and more significant, especially but not only because we now have access to drugs inhibiting complement. After describing the main characteristics of complement biology, both activation of the complement cascade and the many regulatory factors, we will review the precise role of complement in kidney transplant biology. Complement activation has been involved in ischemia-reperfusion injury, in the recurrence of several diseases such as atypical hemolytic uremic syndrome, C3 glomerulopathies, and antiphospholipid syndrome, as well as the process of antibody-mediated rejection, either acute or chronic. There are many potentially interesting drugs interfering with complement inhibition that have been or may be studied in kidney transplantation. Currently, the bulk of data concerns eculizumab, a monoclonal antibody blocking the complement cascade at the C5. Its efficacy has been demonstrated in the treatment and prevention of recurrence of atypical hemolytic uremic syndrome with an overall good safety profile. Although it has been reported to be efficacious to prevent antibody-mediated rejection, properly designed trials are currently being performed to state this efficacy. In addition, randomized trials are, in the process, regarding the prevention of ischemia-reperfusion injury after kidney transplantation.

PROYECTO PROMETEO2

www.prometeo2020.setrasplante.org

Acreditación

Actividad acreditada con 14,2 créditos por la Comisión de Formación Continuada de las Profesiones Sanitarias de Cantabria, con Expediente nº 7.410-274/20

Sede

Hotel Meliá Castilla
c/ del Poeta Joan Maragall, 43
28020 Madrid

Secretaría Científica Publicis Health

División de Publicis Comunicación España
Avda. del Partenón 12-14 | Madrid, 28042
Tel +34 917 684 713
Fax +34 917 684 713

Secretaría de la SET

Pasaje de Peña, 2- 3ºC - 39008 Santander
Tel. +34 902 116 513 - Fax +34 942 231 058

Organizado por

SET SOCIEDAD ESPAÑOLA DE TRASPLANTE

Con la colaboración de

SANDOZ A Novartis Division

NOVARTIS