Bölüm **18**

Akut Hücresel ve Humoral Rejeksiyonların Kliniği, Tanısı ve Tedavisi; Güncel Yaklaşımlar

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Potent immünsupresif ilaçların kullanımıyla, son 3 dekaddır akut rejeksiyon insidansında dramatik bir azalma olmuştur. Renal transplantasyon sonrası 1.yıl akut rejeksiyon insidansı % 10-15 civarındadır ancak hücresel ve humoral rejeksiyon halen allogreft sağkalımını olumsuz etkilemeye devam etmektedir. Akut rejeksiyon ataklarının çoğunluğu T hücre aracılıdır ancak tüm akut rejeksiyon ataklarının yaklaşık % 12-37'sinin humoral komponenti de mevcuttur. Böbrek nakli hastalarının yönetiminde, allogreft rejeksiyonunu önlemek için optimum immünsupresyon seviyesine ulaşmaya çalışırken, bir yandan da ilaç toksisitesinin, yeni gelişen diyabetin, dislipideminin, infeksiyon ve malignitenin önlenmesi için immünsupresif ilaçların minimize edilmesi zorlu bir iştir.

Akut rejeksiyon canlıdan yapılan nakillerde daha iyi uyum olması ve soğuk iskemi zamanının kısa olması sebebiyle, kadavradan yapılan nakillere göre daha az görülür. Akut rejeksiyon gelişimi açısından risk faktörleri; presensitizasyon (Donör Spesifik Antkikor [DSA] varlığı veya yüksek panel reaktif antikor [PRA] varlığı), Human Lökosit Antijen (HLA) mismatch fazlalığı, pediatrik alıcı, Afro-Amerikalılar, kan grubu uyumsuzluğu, uzamış soğuk iskemi zamanı ve gecikmiş greft fonksiyonudur. Ayrıca daha önce rejeksiyon geçirmek, iki veya daha fazla nakil olmak ve ilaca uyumsuzluk akut rejeksiyon için diğer risk faktörleridir.

Akut rejeksiyon atakları uzun dönem allogreft sağkalımında azalma ile ilişkilidir, ancak her rejeksiyon atağı allogreft sağkalımını etkilemez. Rejeksiyonun

Kaynaklar

1. Lebranchu Y, Baan C, Biancone L, Legendre C, Morales JM, Naesens M, Thomusch O, Friend P. Pretransplant identification of acute rejection risk following kidney transplantation. Transpl Int. 2014 Feb;27(2):129-38.
2. Cole EH, Johnston O, Rose CL, Gill JS. Impact of acute rejection and new-onset diabetes on long-term transplant graft and patient survival. Clin J Am Soc Nephrol 2008; 3: 814.
3. Mauyedi S,Covin RB. Humoral rejection in kidney transplantation:new concepts in diagnosis and treatment. Curr Opin Nephrol Hypertens. 2002;11:609-618.
4. Opelz G, Döhler B, Collaborative Transplant Study Report .Influence of time of rejection on long-term graft survival in renal transplantation.Transplantation. 2008;85(5):661.
5. Rush DN, Henry SF, Jeffery JR, Schroeder TJ, Gough J. Histological findings in early routine biopsies of stable renal allograft recipients. Transplantation 1994; 57:208.
6. Ron Shapiro, Parmjeet Randhawa, Mark L. Jordan, Velma P. Scantlebury, Carlos Vivas, Ashok Jain, Robert J. Corry, Jerry McCauley, James Johnston, Joseph Donaldson, Edward A. Gray, Igor Dvorchik, Thomas R. Hakala, John J. Fung, Thomas E. Starzl. Renal allograft rejection with normal renal function in simultaneous kidney/pancreas recipients: does dissynchronous rejection really exist? Transplantation 2000; 69:440.
7. Roberts IS, Reddy S, Russell C, Davies DR, Friend PJ, Handa AI, Morris PJ. Subclinical rejection and borderline changes in early protocol biopsy specimens after renal transplantation. Transplantation 2004; 77:1194.
8. Kee TY, Chapman JR, O'Connell PJ, Fung CL, Allen RD, Kable K, Vitalone MJ, Nankivell BJ.Treatment of subclinical rejection diagnosed by protocol biopsy of kidney transplants. Transplantation 2006; 82:36.
9. Nankivell BJ, Chapman JR. The significance of subclinical rejection and the value of protocol biopsies. Am J Transplant 2006; 6:2006.
10. Scholten EM ,Rowshani AT, Cremers S, Bemelman FJ, Eikmans M, van Kan E, Mallat MJ, Florquin S, Surachno J, ten Berge IJ, Bajema IM, de Fijter JW. Untreated rejection in 6-month protocol biopsies is not associated with fibrosis in serial biopsies or with loss of graft function. J Am Soc Nephrol 2006; 17:2622.
11. Serón D, Moreso F. Protocol biopsies in renal transplantation: prognostic value of structural monitoring. Kidney Int 2007; 72:690.
12. Thaunat O, Legendre C, Morelon E, Kreis H, Mamzer-Bruneel MF. To biopsy or not to biopsy? Should we screen the histology of stable renal grafts? Transplantation 2007; 84:671.
13. Mengel M, Bogers J, Bosmans JL, Serón D, Moreso F, Carrera M, Gwinner W, Schwarz A, De Broe M, Kreipe H, Haller H; ESPRIT group. Incidence of C4d stain in protocol biopsies from renal allografts: results from a multicenter trial. Am J Transplant 2005; 5:1050.
14. Matas AJ, Gaston RS. Moving Beyond Minimization Trials in Kidney Transplantation. J Am Soc Nephrol 2015; 26:2898.

15. Lo DJ, Kaplan B, Kirk AD. Biomarkers for kidney transplant rejection. Nat Rev Nephrol 2014; 10:215.
16. Anglicheau D, Suthanthiran M. Noninvasive prediction of organ graft rejection and outcome using gene expression patterns. Transplantation 2008; 86:192.
17. Anglicheau D, Naesens M, Essig M, Gwinner W, Marquet P. Establishing Biomarkers in Transplant Medicine: A Critical Review of Current Approaches. Transplantation 2016; 100:2024.
18. Naesens M, Sarwal MM. Molecular diagnostics in transplantation. Nat Rev Nephrol 2010; 6:614.
19. Perkins D, Verma M, Park KJ. Advances of genomic science and systems biology in renal transplantation: a review. Semin Immunopathol 2011; 33:211.
20. Traitanon O, Poggio ED, Fairchild RL. Molecular monitoring of alloimmune-mediated injury in kidney transplant patients. Curr Opin Nephrol Hypertens 2014; 23:625.
21. Hricik DE, Rodriguez V, Riley J, Bryan K, Tary-Lehmann M, Greenspan N, Dejelo C, Schulak JA, Heeger PS. Enzyme linked immunosorbent spot (ELISPOT) assay for interferon-gamma independently predicts renal function in kidney transplant recipients. Am J Transplant 2003; 3:878.
22. Augustine JJ, Siu DS, Clemente MJ, Schulak JA, Heeger PS, Hricik DE.Pre-transplant IFN-gamma ELISPOTs are associated with post-transplant renal function in African American renal transplant recipients. Am J Transplant 2005; 5:1971.
23. Kim SH, Oh EJ, Kim MJ, Park YJ, Han K, Yang HJ, Kim JY, Choi BS, Yang CW, Kim YS, Bang BK.Pretransplant donor-specific interferon-gamma ELISPOT assay predicts acute rejection episodes in renal transplant recipients. Transplant Proc 2007; 39:3057.
24. Koscielska-Kasprzak K, Drulis-Fajdasz D, Kaminska D, Mazanowska O, Krajewska M, Gdowska W, Bieniecki W, Chudoba P, Polak W, Janczak D, Patrzalek D, Klinger M. Pretransplantation cellular alloreactivity is predictive of acute graft rejection and 1-year graft function in kidney transplant recipients. Transplant Proc 2009; 41:3006.
25. Näther BJ, Nickel P, Bold G, Presber F, Schönemann C, Pratschke J, Volk HD, Reinke P.Modified ELISPOT technique--highly significant inverse correlation of post-Tx donor-reactive IFNgamma-producing cell frequencies with 6 and 12 months graft function in kidney transplant recipients. Transpl Immunol 2006; 16:232.
26. Nickel P, Presber F, Bold G, Biti D, Schönemann C, Tullius SG, Volk HD, Reinke P.Enzyme-linked immunosorbent spot assay for donor-reactive interferon-gamma-producing cells identifies T-cell presensitization and correlates with graft function at 6 and 12 months in renal-transplant recipients. Transplantation 2004; 78:1640.
27. Roedder S, Sigdel T, Salomonis N, Hsieh S, Dai H, Bestard O, Metes D, Zeevi A, Gritsch A, Cheeseman J, Macedo C, Peddy R, Medeiros M, Vincenti F, Asher N, Salvatierra O, Shapiro R, Kirk A, Reed EF, Sarwal MM. The kSORT assay to detect renal transplant patients at high risk for acute rejection: results of the multicenter AART study. PLoS Med 2014; 11:e1001759.

28. Bloom RD, Bromberg JS, Poggio ED, Bunnapradist S, Langone AJ, Sood P, Matas AJ, Mehta S, Mannon RB, Sharfuddin A, Fischbach B, Narayanan M, Jordan SC, Cohen D, Weir MR, Hiller D, Prasad P, Woodward RN, Grskovic M, Sninsky JJ, Yee JP, Brennan DC; Circulating Donor-Derived Cell-Free DNA in Blood for Diagnosing Active Rejection in Kidney Transplant Recipients (DART) Study Investigators. Cell-Free DNA and Active Rejection in Kidney Allografts. J Am Soc Nephrol 2017; 28:2221.
29. Li B, Hartono C, Ding R, Sharma VK, Ramaswamy R, Qian B, Serur D, Mouradian J, Schwartz JE, Suthanthiran M. Noninvasive diagnosis of renal-allograft rejection by measurement of messenger RNA for perforin and granzyme B in urine. N Engl J Med 2001; 344:947.
30. Muthukumar T, Ding R, Dadhania D, Medeiros M, Li B, Sharma VK, Hartono C, Serur D, Seshan SV, Volk HD, Reinke P, Kapur S, Suthanthiran M.Serine proteinase inhibitor-9, an endogenous blocker of granzyme B/perforin lytic pathway, is hyperexpressed during acute rejection of renal allografts. Transplantation 2003; 75:1565.
31. Ding, Ruchuang; Li, Baogui; Muthukumar, Thangamani; Dadhania, Darshana; Medeiros, Mara; Hartono, Choli; Serur, David; Seshan, Surya V.; Sharma, Vijay K.; Kapur, Sandip; Suthanthiran, Manikkam.CD103 mRNA levels in urinary cells predict acute rejection of renal allografts. Transplantation 2003; 75:1307.
32. Hancock WW, Lu B, Gao W, Csizmadia V, Faia K, King JA, Smiley ST, Ling M, Gerard NP, Gerard C. Requirement of the chemokine receptor CXCR3 for acute allograft rejection. J Exp Med 2000; 192:1515.
33. Lorenzen JM, Volkmann I, Fiedler J, Schmidt M, Scheffner I, Haller H, Gwinner W, Thum T. Urinary miR-210 as a mediator of acute T-cell mediated rejection in renal allograft recipients. Am J Transplant 2011; 11:2221.
34. Hricik DE, Nickerson P, Formica RN, Poggio ED, Rush D, Newell KA, Goebel J, Gibson IW, Fairchild RL, Riggs M, Spain K, Ikle D, Bridges ND, Heeger PS; CTOT-01 consortium. Multicenter validation of urinary CXCL9 as a risk-stratifying biomarker for kidney transplant injury. Am J Transplant 2013; 13:2634.
35. Schaub S, Nickerson P, Rush D, Mayr M, Hess C, Golian M, Stefura W, Hayglass K. Urinary CXCL9 and CXCL10 levels correlate with the extent of subclinical tubulitis. Am J Transplant 2009; 9:1347.
36. Rabant M, Amrouche L, Lebreton X, Aulagnon F, Benon A, Sauvaget V, Bonifay R, Morin L, Scemla A, Delville M, Martinez F, Timsit MO, Duong Van Huyen JP, Legendre C, Terzi F, Anglicheau D.Urinary C-X-C Motif Chemokine 10 Independently Improves the Noninvasive Diagnosis of Antibody-Mediated Kidney Allograft Rejection. J Am Soc Nephrol 2015; 26:2840.
37. Gwinner W, Metzger J, Husi H, Marx D. Proteomics for rejection diagnosis in renal transplant patients: Where are we now? World J Transplant 2016; 6:28.
38. Periera, BJG, Sayegh, MH, Blake, P Diagnosis and therapy of graft dysfunction. In: Chronic kidney disease, dialysis and transplantation, 2, (Eds), Elsevier Saunders, Philadelphia 2005. p.641.

39. Lovinfosse P, Weekers L, Bonvoisin C, Bovy C, Grosch S, Krzesinski JM, Hustinx R, Jouret F. Fluorodeoxyglucose F(18) Positron Emission Tomography Coupled With Computed Tomography in Suspected Acute Renal Allograft Rejection. Am J Transplant 2016; 16:310.
40. Haas M, Sis B, Racusen LC, et al. Banff 2013 meeting report: inclusion of c4d-negative antibody-mediated rejection and antibody-associated arterial lesions. Am J Transplant 2014; 14:272.
41. Haas M, Sis B, Racusen LC, Solez K, Glotz D, Colvin RB, Castro MC, David DS, David-Neto E, Bagnasco SM, Cendales LC, Cornell LD, Demetris AJ, Drachenberg CB, Farver CF, Farris AB 3rd, Gibson IW, Kraus E, Liapis H, Loupy A, Nickeleit V, Randhawa P, Rodriguez ER, Rush D, Smith RN, Tan CD, Wallace WD, Mengel M; Banff meeting report writing committee. The Banff 2017 Kidney Meeting Report: Revised diagnostic criteria for chronic active T cell-mediated rejection, antibody-mediated rejection, and prospects for integrative endpoints for next-generation clinical trials. Am J Transplant 2018; 18:293.
42. Solez K, Axelsen RA, Benediktsson H, Burdick JF, Cohen AH, Colvin RB, Croker BP, Droz D, Dunnill MS, Halloran PF .International standardization of criteria for the histologic diagnosis of renal allograft rejection: the Banff working classification of kidney transplant pathology. Kidney Int 1993; 44:411.
43. Dragun D, Müller DN, Bräsen JH, Fritsche L, Nieminen-Kelhä M, Dechend R, Kintscher U, Rudolph B, Hoebeke J, Eckert D, Mazak I, Plehm R, Schönemann C, Unger T, Budde K, Neumayer HH, Luft FC, Wallukat G. Angiotensin II type 1-receptor activating antibodies in renal-allograft rejection. N Engl J Med 2005; 352:558.
44. Tiriveedhi V, Angaswamy N, Brand D, Weber J, Gelman AG, Hachem R, Trulock EP, Meyers B, Patterson G, Mohanakumar T.A shift in the collagen V antigenic epitope leads to T helper phenotype switch and immune response to self-antigen leading to chronic lung allograft rejection. Clin Exp Immunol 2012; 167:158.
45. Rose ML. Role of anti-vimentin antibodies in allograft rejection. Hum Immunol 2013; 74:1459.
46. Cardinal H, Dieudé M, Brassard N, Qi S, Patey N, Soulez M, Beillevaire D, Echeverry F, Daniel C, Durocher Y, Madore F, Hébert MJ. Antiperlecan antibodies are novel accelerators of immune-mediated vascular injury. Am J Transplant 2013; 13:861.
47. Magil AB. Infiltrating cell types in transplant glomerulitis: relationship to peritubular capillary C4d deposition. Am J Kidney Dis 2005; 45:1084.
48. Habicht A, Regele H, Exner M, Soleiman A, Hörl WH, Watschinger B, Derfler K, Böhmig GA. A case of severe C4d-positive kidney allograft dysfunction in the absence of histomorphologic features of rejection. Wien Klin Wochenschr 2002; 114:945.
49. Dickenmann M, Steiger J, Descoeudres B, Mihatsch M, Nickeleit V. The fate of C4d positive kidney allografts lacking histological signs of acute rejection. Clin Nephrol 2006; 65:173.
50. Mauiyyedi S, Crespo M, Collins AB, et al. Acute humoral rejection in kidney transplantation: II. Morphology, immunopathology, and pathologic classification. J Am Soc Nephrol 2002; 13:779.

51. Sis B, Jhangri GS, Bunnag S, et al. Endothelial gene expression in kidney transplants with alloantibody indicates antibody-mediated damage despite lack of C4d staining. Am J Transplant 2009; 9:2312.
52. Scornik JC, Guerra G, Schold JD, et al. Value of posttransplant antibody tests in the evaluation of patients with renal graft dysfunction. Am J Transplant 2007; 7:1808.
53. Viglietti D, Loupy A, Vernerey D, et al. Value of Donor-Specific Anti-HLA Antibody Monitoring and Characterization for Risk Stratification of Kidney Allograft Loss. J Am Soc Nephrol 2017; 28:702.
54. Mauiyyedi S, Crespo M, Collins AB, Schneeberger EE, Pascual MA, Saidman SL, Tolkoff-Rubin NE, Williams WW, Delmonico FL, Cosimi AB, Colvin RB .Chronic humoral rejection: identification of antibody-mediated chronic renal allograft rejection by C4d deposits in peritubular capillaries. J Am Soc Nephrol 2001; 12:574.
55. Naesens M, Kuypers DR, De Vusser K, Evenepoel P, Claes K, Bammens B, Meijers B, Sprangers B, Pirenne J, Monbaliu D, Jochmans I, Lerut E.The histology of kidney transplant failure: a long-term follow-up study. Transplantation 2014; 98:427.
56. Wu K, Budde K, Schmidt D, Neumayer HH, Rudolph B. The Relationship of the Severity and Category of Acute Rejection With Intimal Arteritis Defined in Banff Classification to Clinical Outcomes. Transplantation 2015; 99:e105.
57. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients.Am J Transplant. 2009 Nov;9 Suppl 3:S1-155.
58. Filo RS, Smith EJ, Leapman SB. Therapy of acute cadaveric renal allograft rejection with adjunctive antithymocyte globulin. Transplantation 1980; 30:445.
59. Hoitsma AJ, Reekers P, Kreeftenberg JG, van Lier HJ, Capel PJ, Koene RA. Treatment of acute rejection of cadaveric renal allografts with rabbit antithymocyte globulin. Transplantation 1982; 33:12.
60. Hoitsma AJ, van Lier HJ, Reekers P, Koene RA. Improved patient and graft survival after treatment of acute rejections of cadaveric renal allografts with rabbit antithymocyte globulin. Transplantation 1985; 39:274.
61. Streem SB, Novick AC, Braun WE, Steinmuller D, Greenstreet R. Low-dose maintenance prednisone and antilymphoblast globulin for the treatment of acute rejection. A steroid-sparing approach to immunosuppressive therapy. Transplantation 1983; 35:420.
62. Webster AC, Wu S, Tallapragada K, Park MY, Chapman JR, Carr SJ. Polyclonal and monoclonal antibodies for treating acute rejection episodes in kidney transplant recipients. Cochrane Database Syst Rev 2017; 7:CD004756.
63. Vo AA, Lukovsky M, Toyoda M, Wang J, Reinsmoen NL, Lai CH, Peng A, Villicana R, Jordan SC.Rituximab and intravenous immune globulin for desensitization during renal transplantation.N Engl J Med. 2008 Jul 17;359(3):242-51.
64. Velidedeoglu E, Cavaillé-Coll MW, Bala S, Belen OA, Wang Y, Albrecht R. Summary of 2017 FDA Public Workshop: Antibody-mediated Rejection in Kidney Transplantation. Transplantation 2018; 102:e257.

65. Perry DK, Burns JM, Pollinger HS, Amiot BP, Gloor JM, Gores GJ, Stegall MD. Proteasome inhibition causes apoptosis of normal human plasma cells preventing alloantibody production. Am J Transplant 2009; 9:201.

66. Nigos JG, Arora S, Nath P, Hussain SM, Marcus RJ, Ko TY, Sureshkumar KK. Treatment of antibody-mediated rejection in kidney transplant recipients: a single-center experience with a bortezomib-based regimen. Exp Clin Transplant 2012; 10:609.

67. Everly MJ, Everly JJ, Susskind B, Brailey P, Arend LJ, Alloway RR, Roy-Chaudhury P, Govil A, Mogilishetty G, Rike AH, Cardi M, Wadih G, Tevar A, Woodle ES.Bortezomib provides effective therapy for antibody- and cell-mediated acute rejection. Transplantation 2008; 86:1754.

68. Flechner SM, Fatica R, Askar M, Stephany BR, Poggio E, Koo A, Banning S, Chiesa-Vottero A, Srinivas T.The role of proteasome inhibition with bortezomib in the treatment of antibody-mediated rejection after kidney-only or kidney-combined organ transplantation. Transplantation 2010; 90:1486.

69. Walsh RC, Everly JJ, Brailey P, Rike AH, Arend LJ, Mogilishetty G, Govil A, Roy-Chaudhury P, Alloway RR, Woodle ES. Proteasome inhibitor-based primary therapy for antibody-mediated renal allograft rejection. Transplantation 2010; 89:277.

70. Walsh RC, Brailey P, Girnita A, Alloway RR, Shields AR, Wall GE, Sadaka BH, Cardi M, Tevar A, Govil A, Mogilishetty G, Roy-Chaudhury P, Woodle ES.Early and late acute antibody-mediated rejection differ immunologically and in response to proteasome inhibition. Transplantation 2011; 91:1218.

71. Yamamoto T, Watarai Y, Futamura K, Okada M, Tsujita M, Hiramitsu T, Goto N, Narumi S, Takeda A, Kobayashi T.Efficacy of Eculizumab Therapy for Atypical Hemolytic Uremic Syndrome Recurrence and Antibody-Mediated Rejection Progress After Renal Transplantation With Preformed Donor-Specific Antibodies: Case Report. Transplant Proc 2017; 49:159.

72. Locke JE, Magro CM, Singer AL, Segev DL, Haas M, Hillel AT, King KE, Kraus E, Lees LM, Melancon JK, Stewart ZA, Warren DS, Zachary AA, Montgomery RA.The use of antibody to complement protein C5 for salvage treatment of severe antibody-mediated rejection. Am J Transplant 2009; 9:231.

73. Kocak B, Arpali E, Demiralp E, Yelken B, Karatas C, Gorcin S, Gorgulu N, Uzunalan M, Turkmen A, Kalayoglu M. Eculizumab for salvage treatment of refractory antibody-mediated rejection in kidney transplant patients: case reports. Transplant Proc 2013; 45:1022.

74. Ghirardo G, Benetti E, Poli F, Vidal E, Della Vella M, Cozzi E, Murer L. Plasmapheresis-resistant acute humoral rejection successfully treated with anti-C5 antibody. Pediatr Transplant 2014; 18:E1.

75. Eskandary F, Wahrmann M, Mühlbacher J, Böhmig GA. Complement inhibition as potential new therapy for antibody-mediated rejection. Transpl Int 2016; 29:392.