Bölüm **7**

Eculizumab, Etki Mekanizması, Endikasyonları ve Nefrolojide Eculizumab Kullanımı

Eray Eroğlu

• GİRİŞ

Eculizumab, 2006 yılında Alexion Pharmaceuticals firması tarafından 300 mg/30 ml konsantre infüzyon çözeltisi olarak üretilen Soliris® ismi ile biyolojik lisansı alınan ve 2007 yılında U.S. Food and Drug Administration (FDA) (Birleşik devletler Gıda ve İlaç Dairesi) tarafından paroksismal nokturnal hemoglobinüri tedavisinde onaylanan kompleman faktör 5 (C5)'in fare kaynaklı insanlaştırılmış monoklonal IgG2/4κ tipinde antikorudur. FDA tarafından 2011 yılında atipik hemolitik üremik sendromda (aHÜS), 2017 yılında ise myastenia gravis hastalığında kullanımı onaylanmıştır. Aynı yıllarda European Medicine Agency (EMA) (Avrupa İlaç Kurumu) tarafından da kullanımı aynı endikasyonlarla onaylanmıştır. Ülkemizde ise 2015 yılında ilaç ruhsatı alınmış olup, 3 yıl süre ile Türkiye İlaç ve Tıbbi Cihaz Kurumu (TİTCK) tarafından endikasyon dışı başvuru kapsamında Türk Ezcacılar Birliği aracılığıyla yurt dışından temin edilerek verilebilen ilaç, 2018 yılında Paroksismal nokturnal hemoglobinüri (PNH) ve aHÜS tedavisinde sosyal güvenlik kurumu tarafından geri ödeme kapsamında endikasyon dâhilinde belirli bölgelerde hastanelerin eczanesinden temin edilerek kullanımına başlanmıştır.

• ETKİ MEKANİZMASI VE YAN ETKİLER

C5, C5 konvertaz ile C5a ve C5b'ye bölünür. C5a vasküler permeabiliteyi arttırır ve kemotaksis ile inflamatuar hücreleri çeker. C5b diğer kompleman komponenetlerine

Kaynaklar

1. Rother RP, Rollins SA, Mojcik CF, Brodsky RA, Bell L. Discovery anddevelopment of the complement inhibitor eculizumab for the treatment ofparoxysmal nocturnal hemoglobinuria. Nat Biotechnol. 2007 Nov;25(11):1256-64.
2. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125166s172lbl.pdf
3. http://alexion.com/products/Soliris
4. Hillmen P, Young NS, Schubert J, Brodsky RA, Socié G, Muus P, Röth A, Szer J, Elebute MO, Nakamura R, Browne P, Risitano AM, Hill A, Schrezenmeier H, Fu CL, Maciejewski J, Rollins SA, Mojcik CF, Rother RP, Luzzatto L. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2006 Sep 21;355(12):1233-43.
5. Applegate AO, Fong VC, Tardivel K, Lippold SA, Zarate S. Notes from the Field: Meningococcal Disease in an International Traveler on Eculizumab Therapy – United States, 2015. MMWR Morb Mortal Wkly Rep. 2016 Jul 15;65(27):696-7.
6. Brodsky RA, Young NS, Antonioli E, Risitano AM, Schrezenmeier H, Schubert J, Gaya A, Coyle L, de Castro C, Fu CL, Maciejewski JP, Bessler M, Kroon HA, Rother RP, Hillmen P. Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria. Blood. 2008 Feb 15;111(4):1840-7.
7. Brodsky RA. Paroxysmal nocturnal hemoglobinuria. Blood. 2014 Oct 30;124(18):2804-11. doi: 10.1182/blood-2014-02-522128.
8. Gustavsen A, Skattum L, Bergseth G, Lorentzen B, Floisand Y, Bosnes V, Mollnes TE, Barratt-Due A. Effect on mother and child of eculizumab given before caesarean section in a patient with severe antiphospholipid syndrome: A case report. Medicine (Baltimore). 2017 Mar;96(11):e6338.
9. Kelly RJ, Höchsmann B, Szer J, Kulasekararaj A, de Guibert S, Röth A, Weitz IC, Armstrong E, Risitano AM, Patriquin CJ, Terriou L, Muus P, Hill A, Turner MP, Schrezenmeier H, Peffault de Latour R. Eculizumab in Pregnant Patients with Paroxysmal Nocturnal Hemoglobinuria. N Engl J Med. 2015 Sep 10;373(11):1032-9.
10. Servais A, Devillard N, Frémeaux-Bacchi V, Hummel A, Salomon L, Contin-Bordes C, Gomer H, Legendre C, Delmas Y. Atypical haemolytic uraemic syndrome and pregnancy: outcome with ongoing eculizumab. Nephrol Dial Transplant. 2016 Dec;31(12):2122-2130.
11. Miyasaka N, Miura O, Kawaguchi T, Arima N, Morishita E, Usuki K, Morita Y,Nishiwaki K, Ninomiya H, Gotoh A, Imashuku S, Urabe A, Shichishima T, Nishimura
12. J, Kanakura Y. Pregnancy outcomes of patients with paroxysmal nocturnal hemoglobinuria treated with eculizumab: a Japanese experience and updated review. Int J Hematol. 2016 Jun;103(6):703-12.
13. Demir E, Yazici H, Ozluk Y, Kilicaslan I, Turkmen A. Pregnant Woman with Atypical Hemolytic Uremic Syndrome Delivered a Healthy Newborn under Eculizumab Treatment. Case Rep Nephrol Dial. 2016 Dec 20;6(3):143-148.

14. Huerta A, Arjona E, Portoles J, Lopez-Sanchez P, Rabasco C, Espinosa M, Cavero T, Blasco M, Cao M, Manrique J, Cabello-Chavez V, Suñer M, Heras M, Fulladosa X, Belmar L, Sempere A, Peralta C, Castillo L, Arnau A, Praga M, Rodriguez de Cordoba S. A retrospective study of pregnancy-associated atypical hemolytic uremic syndrome. Kidney Int. 2018 Feb;93(2):450-459.
15. Lindorfer MA, Pawluczkowycz AW, Peek EM, Hickman K, Taylor RP, Parker CJ. A novel approach to preventing the hemolysis of paroxysmal nocturnal hemoglobinuria: both complement-mediated cytolysis and C3 deposition are blocked by a monoclonal antibody specific for the alternative pathway of complement. Blood. 2010 Mar 18;115(11):2283-91.
16. Hillmen P, Muus P, Röth A, Elebute MO, Risitano AM, Schrezenmeier H, Szer J, Browne P, Maciejewski JP, Schubert J, Urbano-Ispizua A, de Castro C, Socié G, Brodsky RA. Long-term safety and efficacy of sustained eculizumab treatment in patients with paroxysmal nocturnal haemoglobinuria. Br J Haematol. 2013 Jul;162(1):62-73.
17. Hillmen P, Muus P, Dührsen U, Risitano AM, Schubert J, Luzzatto L, Schrezenmeier H, Szer J, Brodsky RA, Hill A, Socié G, Bessler M, Rollins SA, Bell L, Rother RP, Young NS. Effect of the complement inhibitor eculizumab on thromboembolism in patients with paroxysmal nocturnal hemoglobinuria. Blood. 2007 Dec 1;110(12):4123-8.
18. DeZern AE, Dorr D, Brodsky RA. Predictors of hemoglobin response to eculizumab therapy in paroxysmal nocturnal hemoglobinuria. Eur J Haematol. 2013 Jan;90(1):16-24. doi: 10.1111/ejh.12021.
19. Nishimura J, Yamamoto M, Hayashi S, Ohyashiki K, Ando K, Brodsky AL, Noji H, Kitamura K, Eto T, Takahashi T, Masuko M, Matsumoto T, Wano Y, Shichishima T, Shibayama H, Hase M, Li L, Johnson K, Lazarowski A, Tamburini P, Inazawa J, Kinoshita T, Kanakura Y. Genetic variants in C5 and poor response to eculizumab. N Engl J Med. 2014 Feb 13;370(7):632-9.
20. Rondelli T, Risitano AM, Peffault de Latour R, Sica M, Peruzzi B, Ricci P, Barcellini W, Iori AP, Boschetti C, Valle V, Frémeaux-Bacchi V, De Angioletti M, Socie G, Luzzatto L, Notaro R. Polymorphism of the complement receptor 1 gene correlates with the hematologic response to eculizumab in patients with paroxysmal nocturnal hemoglobinuria. Haematologica. 2014 Feb;99(2):262-6.
21. Noris M, Remuzzi G. Hemolytic uremic syndrome. J Am Soc Nephrol. 2005 Apr;16(4):1035-50.
22. Noris M, Remuzzi G. Atypical hemolytic-uremic syndrome. N Engl J Med. 2009 Oct 22;361(17):1676-87.
23. Taylor CM, Machin S, Wigmore SJ, Goodship TH; working party from the Renal Association, the British Committee for Standards in Haematology and the British Transplantation Society. Clinical practice guidelines for the management of atypical haemolytic uraemic syndrome in the United Kingdom. Br J Haematol. 2010 Jan;148(1):37-47.
24. Waters AM, Licht C. aHUS caused by complement dysregulation: new therapies on the horizon. Pediatr Nephrol. 2011 Jan;26(1):41-57.

25. De Yao J, Kaplan R, Magro C. An Atypical Case of Atypical Hemolytic Uremic Syndrome: Predominant Gastrointestinal Involvement, Intact Renal Function, and C5b-9 Deposition in colon and skin. J Hematol 2015, 4:193–195
26. Stühlinger W, Kourilsky O, Kanfer A, Sraer JD. Letter: Haemolytic-uraemic syndrome: evidence for intravascular C3 activation. Lancet. 1974 Sep 28;2(7883):788-9.
27. Barré P, Kaplan BS, de Chadarévian JP, Drummond KN. Hemolytic uremic syndrome with hypocomplementemia, serum C3NeF, and glomerülar deposits of C3. Arch Pathol Lab Med. 1977 Jul;101(7):357-61.
28. Thompson RA, Winterborn MH. Hypocomplementaemia due to a genetic deficiency of beta 1H globulin. Clin Exp Immunol 1981;46:110-9.
29. Rougier N, Kazatchkine MD, Rougier JP, Fremeaux-Bacchi V, Blouin J, Deschenes G, Soto B, Baudouin V, Pautard B, Proesmans W, Weiss E, Weiss L. Human complement factor H deficiency associated with hemolytic uremic syndrome. J Am Soc Nephrol. 1998 Dec;9(12):2318-26.
30. Noris M, Brioschi S, Caprioli J, Todeschini M, Bresin E, Porrati F, Gamba S, Remuzzi G; International Registry of Recurrent and Familial HUS/TTP. Familial haemolytic uraemic syndrome and an MCP mutation. Lancet. 2003 Nov 8;362(9395):1542-7.
31. Bienaime F, Dragon-Durey MA, Regnier CH, Nilsson SC, Kwan WH, Blouin J, Jablonski M, Renault N, Rameix-Welti MA, Loirat C, Sautés-Fridman C, Villoutreix BO, Blom AM, Fremeaux-Bacchi V. Mutations in components of complement influence the outcome of Factor I-associated atypical hemolytic uremic syndrome. Kidney Int. 2010 Feb;77(4):339-49.
32. Sellier-Leclerc AL, Fremeaux-Bacchi V, Dragon-Durey MA, Macher MA, Niaudet P, Guest G, Boudailliez B, Bouissou F, Deschenes G, Gie S, Tsimaratos M, Fischbach M, Morin D, Nivet H, Alberti C, Loirat C; French Society of Pediatric Nephrology. Differential impact of complement mutations on clinical characteristics in atypical hemolytic uremic syndrome. J Am Soc Nephrol. 2007 Aug;18(8):2392-400.
33. Schramm EC, Roumenina LT, Rybkine T, Chauvet S, Vieira-Martins P, Hue C, Maga T, Valoti E, Wilson V, Jokiranta S, Smith RJ, Noris M, Goodship T, Atkinson JP, Fremeaux-Bacchi V. Mapping interactions between complement C3 and regulators using mutations in atypical hemolytic uremic syndrome. Blood. 2015 Apr 9;125(15):2359-69.
34. Goicoechea de Jorge E, Harris CL, Esparza-Gordillo J, Carreras L, Arranz EA, Garrido CA, López-Trascasa M, Sánchez-Corral P, Morgan BP, Rodríguez de Córdoba S. Gain-of-function mutations in complement factor B are associated with atypical hemolytic uremic syndrome. Proc Natl Acad Sci U S A. 2007 Jan 2;104(1):240-5.
35. Delvaeye M, Noris M, De Vriese A, Esmon CT, Esmon NL, Ferrell G, Del-Favero J, Plaisance S, Claes B, Lambrechts D, Zoja C, Remuzzi G, Conway EM. Thrombomodulin mutations in atypical hemolytic-uremic syndrome. N Engl J Med. 2009 Jul 23;361(4):345-57.
36. Moore I, Strain L, Pappworth I, Kavanagh D, Barlow PN, Herbert AP, Schmidt CQ, Staniforth SJ, Holmes LV, Ward R, Morgan L, Goodship TH, Marchbank KJ. Association of factor H autoantibodies with deletions of CFHR1, CFHR3, CFHR4, and with

mutations in CFH, CFI, CD46, and C3 in patients with atypical hemolytic uremic syndrome. Blood. 2010 Jan 14;115(2):379-87.

37. Loirat C, Fakhouri F, Ariceta G, Besbas N, Bitzan M, Bjerre A, Coppo R, Emma F, Johnson S, Karpman D, Landau D, Langman CB, Lapeyraque AL, Licht C, Nester C, Pecoraro C, Riedl M, van de Kar NC, Van de Walle J, Vivarelli M, Frémeaux-Bacchi V; HUS International. An international consensus approach to the management of atypical hemolytic uremic syndrome in children. Pediatr Nephrol. 2016 Jan;31(1):15-39.
38. Rathbone J, Kaltenthaler E, Richards A, Tappenden P, Bessey A, Cantrell A. A systematic review of eculizumab for atypical haemolytic uraemic syndrome (aHUS). BMJ Open. 2013 Nov 4;3(11):e003573.
39. Legendre CM, Licht C, Muus P, Greenbaum LA, Babu S, Bedrosian C, Bingham C,Cohen DJ, Delmas Y, Douglas K, Eitner F, Feldkamp T, Fouque D, Furman RR, GaberO, Herthelius M, Hourmant M, Karpman D, Lebranchu Y, Mariat C, Menne J, Moulin B,Nürnberger J, Ogawa M, Remuzzi G, Richard T, Sberro-Soussan R, Severino B,Sheerin NS, Trivelli A, Zimmerhackl LB, Goodship T, Loirat C. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. N Engl J Med. 2013Jun 6;368(23):2169-81.
40. Licht C, Greenbaum LA, Muus P, Babu S, Bedrosian CL, Cohen DJ, Delmas Y, Douglas K, Furman RR, Gaber OA, Goodship T, Herthelius M, Hourmant M, Legendre CM, Remuzzi G, Sheerin N, Trivelli A, Loirat C. Efficacy and safety of eculizumab in atypical hemolytic uremic syndrome from 2-year extensions of phase 2 studies. Kidney Int. 2015 May;87(5):1061-73.
41. Ardissino G, Tel F, Sgarbanti M, Cresseri D, Giussani A, Griffini S, Grovetto E, Possenti I, Perrone M, Testa S, Paglialonga F, Messa P, Cugno M. Complement functional tests for monitoring eculizumab treatment in patients with atypical hemolytic uremic syndrome: an update. Pediatr Nephrol. 2018 Mar;33(3):457-461.
42. Ardissino G, Testa S, Possenti I, Tel F, Paglialonga F, Salardi S, Tedeschi S, Belingheri M, Cugno M. Discontinuation of eculizumab maintenance treatment for atypical hemolytic uremic syndrome: a report of 10 cases. Am J Kidney Dis. 2014 Oct;64(4):633-7.
43. Merrill SA, Brittingham ZD, Yuan X, Moliterno AR, Sperati CJ, Brodsky RA. Eculizumab cessation in atypical hemolytic uremic syndrome. Blood. 2017 Jul 20;130(3):368-372. doi: 10.1182/blood-2017-02-770214.
44. Kwon T, Dragon-Durey MA, Macher MA, Baudouin V, Maisin A, Peuchmaur M, Fremeaux-Bacchi V, Loirat C. Successful pre-transplant management of a patient with anti-factor H autoantibodies-associated haemolytic uraemic syndrome. Nephrol Dial Transplant. 2008 Jun;23(6):2088-90.
45. Zimmerhackl LB, Hofer J, Cortina G, Mark W, Würzner R, Jungraithmayr TC, Khursigara G, Kliche KO, Radauer W. Prophylactic eculizumab after renal transplantation in atypical hemolytic-uremic syndrome. N Engl J Med. 2010 May 6;362(18):1746-8.
46. Zuber J, Le Quintrec M, Krid S, Bertoye C, Gueutin V, Lahoche A, Heyne N, Ardissino G, Chatelet V, Noël LH, Hourmant M, Niaudet P, Frémeaux-Bacchi V, Rondeau E,

Legendre C, Loirat C; French Study Group for Atypical HUS. Eculizumab for atypical hemolytic uremic syndrome recurrence in renal transplantation. Am J Transplant. 2012 Dec;12(12):3337-54.

47. Saland J. Liver-kidney transplantation to cure atypical HUS: still an option post-eculizumab? Pediatr Nephrol. 2014 Mar;29(3):329-32.
48. Lapeyraque AL, Malina M, Fremeaux-Bacchi V, Boppel T, Kirschfink M, Oualha M, Proulx F, Clermont MJ, Le Deist F, Niaudet P, Schaefer F. Eculizumab in severe Shiga-toxin-associated HUS. N Engl J Med. 2011 Jun 30;364(26):2561-3.
49. Delmas Y, Vendrely B, Clouzeau B, Bachir H, Bui HN, Lacraz A, Hélou S, Bordes C, Reffet A, Llanas B, Skopinski S, Rolland P, Gruson D, Combe C. Outbreak of Escherichia coli O104:H4 haemolytic uraemic syndrome in France: outcome with eculizumab. Nephrol Dial Transplant. 2014 Mar;29(3):565-72.
50. Pape L, Hartmann H, Bange FC, Suerbaum S, Bueltmann E, Ahlenstiel-Grunow T. Eculizumab in Typical Hemolytic Uremic Syndrome (HUS) With Neurological Involvement. Medicine (Baltimore). 2015 Jun;94(24):e1000.
51. Gitiaux C, Krug P, Grevent D, Kossorotoff M, Poncet S, Eisermann M, Oualha M, Boddaert N, Salomon R, Desguerre I. Brain magnetic resonance imaging pattern and outcome in children with haemolytic-uraemic syndrome and neurological impairment treated with eculizumab. Dev Med Child Neurol. 2013 Aug;55(8):758-65.
52. Kemper MJ. Outbreak of hemolytic uremic syndrome caused by E. coli O104:H4 in Germany: a pediatric perspective. Pediatr Nephrol. 2012 Feb;27(2):161-4.
53. Menne J, Nitschke M, Stingele R, Abu-Tair M, Beneke J, Bramstedt J, Bremer JP, Brunkhorst R, Busch V, Dengler R, Deuschl G, Fellermann K, Fickenscher H, Gerigk C, Goettsche A, Greeve J, Hafer C, Hagenmüller F, Haller H, Herget-Rosenthal S, Hertenstein B, Hofmann C, Lang M, Kielstein JT, Klostermeier UC, Knobloch J, Kuehbacher M, Kunzendorf U, Lehnert H, Manns MP, Menne TF, Meyer TN, Michael C, Münte T, Neumann-Grutzeck C, Nuernberger J, Pavenstaedt H, Ramazan L, Renders L, Repenthin J, Ries W, Rohr A, Rump LC, Samuelsson O, Sayk F, Schmidt BM, Schnatter S, Schöcklmann H, Schreiber S, von Seydewitz CU, Steinhoff J, Stracke S, Suerbaum S, van de Loo A, Vischedyk M, Weissenborn K, Wellhöner P, Wiesner M, Zeissig S, Büning J, Schiffer M, Kuehbacher T; EHEC-HUS consortium. Validation of treatment strategies for enterohaemorrhagic Escherichia coli O104:H4 induced haemolytic uraemic syndrome: case-control study. BMJ. 2012 Jul 19;345:e4565.
54. Thurman JM, Marians R, Emlen W, Wood S, Smith C, Akana H, Holers VM, Lesser M, Kline M, Hoffman C, Christen E, Trachtman H. Alternative pathway of complement in children with diarrhea-associated hemolytic uremic syndrome. Clin J Am Soc Nephrol. 2009 Dec;4(12):1920-4.
55. Orth D, Khan AB, Naim A, Grif K, Brockmeyer J, Karch H, Joannidis M, Clark SJ, Day AJ, Fidanzi S, Stoiber H, Dierich MP, Zimmerhackl LB, Würzner R. Shiga toxin activates complement and binds factor H: evidence for an active role of complement in hemolytic uremic syndrome. J Immunol. 2009 May 15;182(10):6394-400.

56. Poolpol K, Orth-Höller D, Speth C, Zipfel PF, Skerka C, de Córdoba SR, Brockmeyer J, Bielaszewska M, Würzner R. Interaction of Shiga toxin 2 with complement regulators of the factor H protein family. Mol Immunol. 2014 Mar;58(1):77-84.
57. Smith RJ, Alexander J, Barlow PN, Botto M, Cassavant TL, Cook HT, de Córdoba SR, Hageman GS, Jokiranta TS, Kimberling WJ, Lambris JD, Lanning LD, Levidiotis V, Licht C, Lutz HU, Meri S, Pickering MC, Quigg RJ, Rops AL, Salant DJ, Sethi S, Thurman JM, Tully HF, Tully SP, van der Vlag J, Walker PD, Würzner R, Zipfel PF; Dense Deposit Disease Focus Group. New approaches to the treatment of dense deposit disease. J Am Soc Nephrol. 2007 Sep;18(9):2447-56.
58. Goodship TH, Cook HT, Fakhouri F, Fervenza FC, Frémeaux-Bacchi V, Kavanagh D, Nester CM, Noris M, Pickering MC, Rodríguez de Córdoba S, Roumenina LT, Sethi S, Smith RJ; Conference Participants. Atypical hemolytic uremic syndrome and C3 glomerülopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. Kidney Int. 2017 Mar;91(3):539-551.
59. Barbour TD, Pickering MC, Terence Cook H. Dense deposit disease and C3glomerülopathy. Semin Nephrol. 2013 Nov;33(6):493-507.
60. Servais A, Frémeaux-Bacchi V, Lequintrec M, Salomon R, Blouin J, Knebelmann B, Grünfeld JP, Lesavre P, Noël LH, Fakhouri F. Primary glomerülonephritis with isolated C3 deposits: a new entity which shares common genetic risk factors with haemolytic uraemic syndrome. J Med Genet. 2007 Mar;44(3):193-9.
61. Bomback AS, Smith RJ, Barile GR, Zhang Y, Heher EC, Herlitz L, Stokes MB, Markowitz GS, D'Agati VD, Canetta PA, Radhakrishnan J, Appel GB. Eculizumab for dense deposit disease and C3 glomerülonephritis. Clin J Am Soc Nephrol. 2012 May;7(5):748-56.
62. McCaughan JA, O'Rourke DM, Courtney AE. Recurrent dense deposit disease after renal transplantation: an emerging role for complementary therapies. Am J Transplant. 2012 Apr;12(4):1046-51.
63. Herlitz LC, Bomback AS, Markowitz GS, Stokes MB, Smith RN, Colvin RB, Appel GB, D'Agati VD. Pathology after eculizumab in dense deposit disease and C3 GN. J Am Soc Nephrol. 2012 Jul;23(7):1229-37.
64. Regunathan-Shenk R, Avasare RS, Ahn W, Canetta PA, Cohen DJ, Appel GB, Bomback AS. Kidney Transplantation in C3 Glomerülopathy: A Case Series. Am J Kidney Dis. 2018 Nov 7. pii: S0272-6386(18)30978-8.
65. Sahin H, Gok Oguz E, Akoglu H, Atilgan G, Ulusal Okyay G, Karaveli Gursoy G, Kip Teymur T, Ertoy D, Canbakan B, Ayli MD. Successful Treatment of Posttransplant Recurrent Complement C3 Glomerülopathy with Eculizumab. Iran J Kidney Dis. 2018 Oct;12(5):315-318.
66. Le Quintrec M, Lapeyraque AL, Lionet A, Sellier-Leclerc AL, Delmas Y, Baudouin V, Daugas E, Decramer S, Tricot L, Cailliez M, Dubot P, Servais A, Mourey-Epron C, Pourcine F, Loirat C, Frémeaux-Bacchi V, Fakhouri F. Patterns of Clinical Response to Eculizumab in Patients With C3 Glomerülopathy. Am J Kidney Dis. 2018 Jul;72(1):84-92.

67. Welte T, Arnold F, Kappes J, Seidl M, Häffner K, Bergmann C, Walz G, Neumann-Haefelin E. Treating C3 glomerülopathy with eculizumab. BMC Nephrol. 2018 Jan 12;19(1):7.
68. Djamali A, Kaufman DB, Ellis TM, Zhong W, Matas A, Samaniego M. Diagnosis and management of antibody-mediated rejection: current status and novel approaches. Am J Transplant. 2014 Feb;14(2):255-71.
69. Farkash EA, Colvin RB. Diagnostic challenges in chronic antibody-mediated rejection. Nat Rev Nephrol. 2012 Mar 27;8(5):255-7.
70. 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 Jan;9(1):231-5.
71. 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 Apr;45(3):1022-5.
72. 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 Feb;18(1):E1-5.
73. Orandi BJ, Zachary AA, Dagher NN, Bagnasco SM, Garonzik-Wang JM, Van Arendonk KJ, Gupta N, Lonze BE, Alachkar N, Kraus ES, Desai NM, Locke JE, Racusen LC, Segev DL, Montgomery RA. Eculizumab and splenectomy as salvage therapy for severe antibody-mediated rejection after HLA-incompatible kidney transplantation. Transplantation. 2014 Oct 27;98(8):857-63.
74. Cornell LD, Schinstock CA, Gandhi MJ, Kremers WK, Stegall MD. Positive cross match kidney transplant recipients treated with eculizumab: outcomes beyond 1 year. Am J Transplant. 2015 May;15(5):1293-302.
75. Röth A, Hüttmann A, Rother RP, Dührsen U, Philipp T. Long-term efficacy of the complement inhibitor eculizumab in cold agglutinin disease. Blood. 2009 Apr 16;113(16):3885-6.