Glomerular Diseases

Case Report

Glomerular Dis 2022;2:100–105
DOI: 10.1159/000520387

Received: June 25, 2021
Accepted: October 17, 2021
Published online: October 22, 2021

Repository Corticotropin in Treating de novo C3 Glomerulonephritis after Transplantation

Muhammad Saad Naseer Ayush Singh Neeraj Singh

Department of Transplant, John C. McDonald Regional Transplant Center-Willis Knighton Health System, Shreveport, LA, USA

Keywords
C3 glomerulopathy · Glomerulonephritis · Renal transplant · Eculizumab · Repository corticotropin · Acthar®

Abstract
Introduction: De novo C3 glomerulonephritis (C3GN) after transplant is uncommon. Although eculizumab has been used successfully in several cases, the response is heterogeneous, and treatment strategies remain undefined. The use of repository corticotropin in C3GN has not been described in the literature. ***Case Report:*** A 48-year-old African American male with kidney transplantation secondary to presumed diabetic nephropathy presented 6 years after transplant with lower extremity edema and nephrotic range proteinuria. His urine protein to creatinine ratio (UPCR) was 8.2 g/g. Renal allograft biopsy confirmed the diagnosis of C3GN. He was treated with eculizumab (Solaris®) 900 mg IV once weekly for 4 weeks and repository corticotropin (H.P. Acthar® gel) 80 units SQ twice weekly for 6 months with a near-complete resolution of proteinuria within 3 months of the treatment. The patient presented again 6 months after completing the therapy with a recurrence of proteinuria, which peaked at 11.6 g/g of UPCR. Repeat kidney allograft biopsy was consistent with C3GN. He was started on repository corticotropin 80 units SQ twice weekly, which resulted in a reduction of proteinuria to >50% within 2 months of therapy. When eculizumab 900 mg IV weekly for 4 weeks was added with repository corticotropin, the proteinuria resolved within 10 weeks of treatment. The patient was maintained on monotherapy of repository corticotropin and has been in complete remission of proteinuria for more than a year until his last follow-up. ***Conclusion:*** This is the first case report describing the role of repository corticotropin as an effective therapy in reducing proteinuria and maintaining patients with C3GN in proteinuria remission.

© 2021 The Author(s).
Published by S. Karger AG, Basel

Introduction

Complement 3 glomerulopathy (C3G) is a rare kidney disease presenting with proteinuria, hematuria, hypertension, or progressive renal failure. It has an estimated incidence of 1–2 cases per million US population [1]. C3G is a disorder of uncontrolled activation of the alternative complement pathway (ACP) that affects glomeruli. This pathway is constantly active at a low level through spontaneous hydrolysis of C3 protein [2]. It is regulated by 2 plasma proteins, factor H (FH) and factor I (FI), and 3 membrane proteins, membrane cofactor protein

karger@karger.com
www.karger.com/gdz

© 2021 The Author(s).
Published by S. Karger AG, Basel

This is an Open Access article licensed under the Creative Commons Attribution-NonCommercial-4.0 International License (CC BY-NC) (http://www.karger.com/Services/OpenAccessLicense), applicable to the online version of the article only. Usage and distribution for commercial purposes requires written permission.

Correspondence to:
Neeraj Singh, nsingh75@hotmail.com

(MCP), decay accelerating factor (DAF), and complement receptor 1 (CR1). The causes of complement dysregulation can be divided into genetic and acquired causes. Any mutation in these regulatory proteins that reduce their ability to control the complement system can lead to the development of C3G. In addition, these genetic defects can be inherited or noninherited. Acquired causes include the development of specific autoantibodies, most notably C3 nephritic factor, that impair regulation of the complement system. C3G is pathologically defined by the deposition of complement protein C3 or its fragments in the glomerulus. Although there may be small amounts of immunoglobulins, the intensity of C3 deposits is twofold or higher than the intensity of immunoglobulins on immunofluorescence [3]. C3G is further subclassified into dense deposit disease and C3 glomerulonephritis (C3GN) on the findings of electron microscopy (EM). Dense deposit disease is distinguished by the presence of intramembranous electron-dense deposits, whereas in C3GN, the deposits are less dense and are found in the mesangium and capillary walls at subendothelial and subepithelial locations. Clinically, both diseases present in a similar manner [4].

C3GN in allografts after kidney transplantation can either occur as a recurrence of the original disease in the native kidney or as de novo, i.e., with no relation to the native kidney disease [5]. C3GN is a rare kidney disease, and its presence in kidney transplant patients is extremely uncommon. There are no randomized control trials to establish a definitive treatment. Management is based on case reports, case series, and the clinical expertise of authors and reviewers. Due to its rarity and absence of established management strategies, de novo C3GN after kidney transplant can be challenging to manage. Sahin et al. [6] reported using eculizumab 900 mg intravenous weekly for 4 weeks followed by a maintenance dose of 1,200 mg intravenous every other week for 9 months in a patient with recurrent C3G after kidney transplant. The patient had complete remission of proteinuria. Welte et al. [7] described the use of eculizumab in 7 patients diagnosed with C3GN. They concluded that early diagnosis and continuous treatment would improve outcomes of C3GN, and eculizumab may be successful in only a subset of patients. Le Quintrec et al. [8] described the use of eculizumab (median duration of treatment, 14 months) in 26 patients with C3G where 6 showed a global clinical response (23%), 6 showed a partial response (23%), and 14 showed no response (54%). They concluded that eculizumab is effective in crescentic rapidly progressive C3G. Finally, an open-label, proof of concept, efficacy, and safety trial of eculizumab in 6 patients with C3GN showed a positive response in 3 patients and stable laboratory parameters with histopathological improvement in 1 patient [9]. The repository corticotropin is approved by the Food and Drug Administration to induce diuresis or remission of proteinuria in nephrotic syndromes [10] and has been used after kidney transplantation in recurrent focal segmental glomerulosclerosis [11] or transplant glomerulopathy [12]. However, the use of repository corticotropin has not been described in C3GN. Here, we describe a patient with de novo C3GN after kidney transplant successfully treated with a combination of eculizumab (Solaris®; Alexion Pharmaceuticals, Cheshire, CT, USA) and repository corticotropin (H.P. Acthar® gel; Mallinckrodt Pharmaceuticals, Hazelwood, MO, USA).

Case Report

A 48-year-old African American male with end-stage renal disease secondary to presumed diabetic nephropathy, as the patient had concomitant retinopathy and neuropathy, underwent deceased donor kidney transplantation in June 2012. After transplant, his serum creatinine reached a nadir of 1.2 mg/dL, and random spot urine protein to creatinine ratio (UPCR) checked multiple times after transplant were all in the range of 0.2–0.3 g/g. He was maintained on tacrolimus 9 mg orally BID, mycophenolate mofetil 1,000 mg orally BID, and prednisone 2.5 mg orally once daily. The patient maintained an uneventful posttransplant course until March 2018, when he presented with lower extremity edema and sudden-onset nephrotic range proteinuria, which peaked at 8.2 g/g of UPCR. His immunosuppressive medications included tacrolimus 0.5 mg orally BID, mycophenolate mofetil 750 mg orally BID, and prednisone 2.5 mg orally once daily. His tacrolimus level was 8.0 ng/mL, and serum creatinine had increased to 2.8 mg/dL. A kidney allograft biopsy was negative for rejection but showed a membranoproliferative pattern with large subendothelial C3 deposits on EM, suggestive of C3GN (Fig. 1). The serum C3 was 90 mg/dL (88–165 mg/dL), serum C4 was 27 mg/dL (14–44 mg/dL), serum C3 nephritic factor ratio was 0.03 (0.00–0.33 ratio), serum FH levels were 171 μg/mL (160–412 μg/mL), and serum anti-FH antibodies were negative (0–7.3% of standard deviation). Soluble C5b-9 level and C4 nephritic factor were not ordered. The patient was started on eculizumab 900 mg intravenous weekly for 4 weeks and Acthar® 80 units subcutaneous twice weekly. His serum creatinine improved, and UPCR came down to 0.80 g/g over the next 3 months. His tacrolimus level at that time was 4.5 ng/mL. However, Acthar® had to be discontinued by the end of October 2018 as the patient developed *Pneumocystis jirovecii* pneumonia. In April 2019, the patient presented with lower extremity edema and recurrent nephrotic range proteinuria of 11.6 g/g of UPCR. At that time, his immunosuppression was maintained on tacrolimus 1 mg orally BID, mycophenolate mofetil 250 mg orally BID, and prednisone 2.5 mg orally once daily. His tacrolimus level was 4.4 ng/ml. A repeat kidney allograft biopsy was consistent with C3GN, with

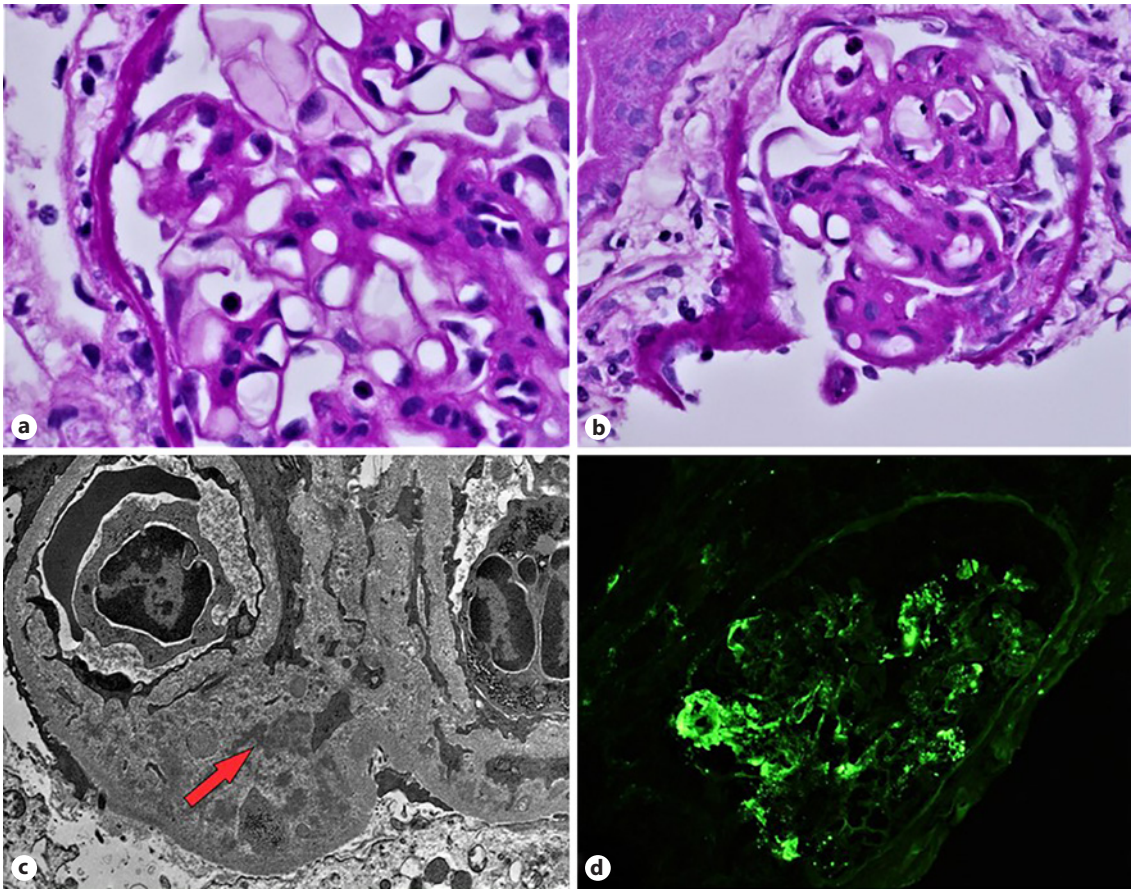

Fig. 1. a, **b** Periodic acid-Schiff shows a membranoproliferative pattern. **c** Electron microscopy showing large subendothelial deposits (red arrow). **d** Immunofluorescence shows a strong C3 reaction of mesangial and capillary walls.

no changes in the amount of C3 deposits on EM compared to the previous biopsy. Acthar® was resumed at 80 units subcutaneous twice weekly. The proteinuria decreased to a nadir of 4.4 g/g of UPCR after 2 months of therapy. Eculizumab 900 mg intravenous weekly for 4 weeks was added alongside Acthar® in October 2019, and after 2 months, proteinuria had decreased to 0.41 g/g of UPCR. The patient has been continued on monotherapy of Acthar® 40 units subcutaneous twice weekly without maintenance eculizumab, which has led to near-complete remission of proteinuria with UPCR ranging from 0.23 to 0.60 g/g for more than a year until his last follow-up. His serum creatinine has stayed stable in the range of 1.4–1.6 mg/dL. Figure 2 outlines the timeline of the clinical course and treatment response of the patient.

Discussion

To our knowledge, this is the first reported case describing the use of repository corticotropin in the management of C3GN after kidney transplantation, either as a combined treatment regimen with eculizumab in the induction therapy or as a monotherapy for maintenance. Duineveld et al. [13] have proposed 2 pathways for ACP dysregulation, a C5-dependent and a C5-independent pathway, and concluded that C3 might play a role, either through C3a-receptor activation or C3dg fragment deposition, in the C5-independent pathway resulting in proteinuria and podocyte damage [14]. It may also explain why eculizumab, a humanized monoclonal antibody targeted against C5, works only in a subset of patients with C3GN since its effect is limited to the C5-dependent pathway in ACP dysregulation. Nevertheless, eculizumab was effective in our patient, suggesting that the underlying pathophysiological mechanism of ACP dysregulation was through C5-dependent pathways.

The exact mechanism of action of repository corticotropin in inducing proteinuria remission in nephrotic syndromes is unknown. Repository corticotropin binds

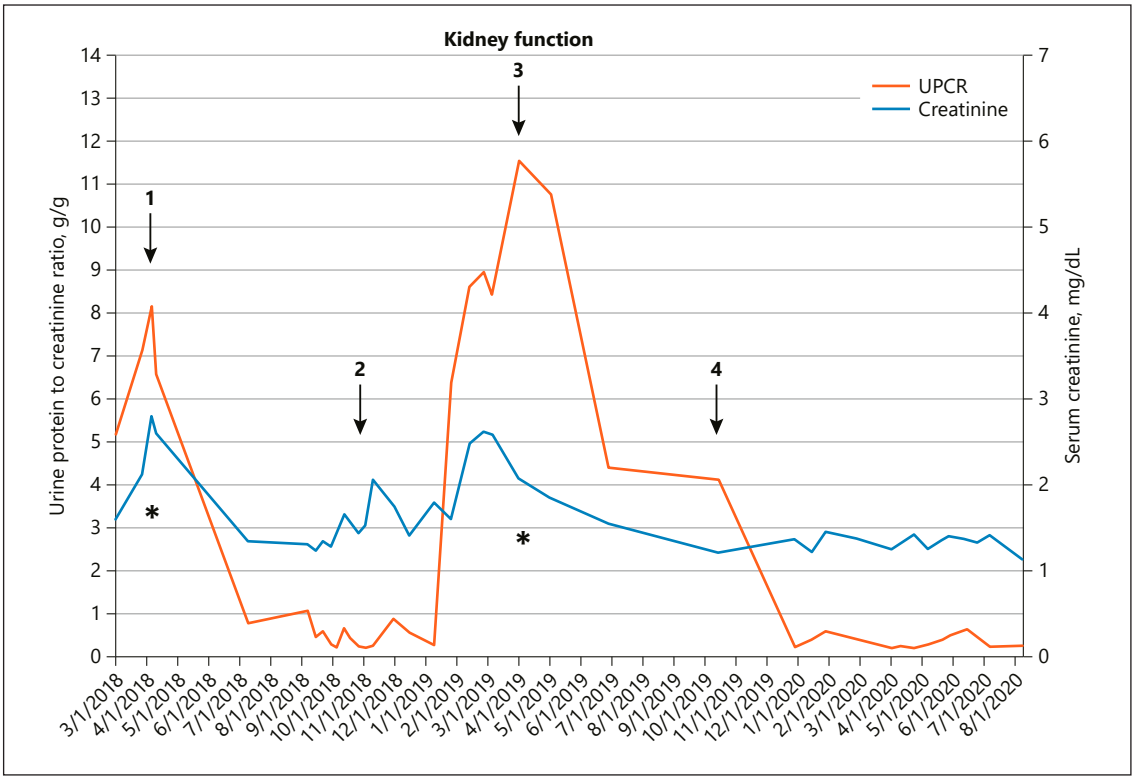

Fig. 2. Timeline of the clinical course and treatment response of the patient. The star indicates the time when the renal allograft biopsies were done. Arrow 1: eculizumab 900 mg IV once weekly for 4 weeks + Acthar® 80 units SQ twice weekly. Arrow 2: Acthar® discontinued. Arrow 3: Acthar® 80 units SQ twice weekly started. Arrow 4: eculizumab 900 mg IV once weekly for 4 weeks followed by a maintenance dose of Acthar® 40 units SQ twice weekly.

to melanocortin receptors MCR (1–5) distributed throughout the body. In addition to its binding to melanocortin-2 receptors (MC2R) present in the adrenal cortex to regulate synthesis and release of glucocorticoids, it binds to MCRs in the kidney, liver, CNS cells, and immune cells. In the kidneys, it binds to MC1R, MC2R, MC3R, MC4R, and MC5R at tubular cells, endothelial cells, mesangial cells, and podocytes [15]. However, its renoprotective effect is from its binding with MC1Rs, which are most abundantly present on podocytes and are overexpressed in response to podocyte injury [16, 17]. Thus, it stabilizes the podocyte actin cytoskeleton, resulting in decreased oxidative stress, reduced podocyte foot process effacement and apoptosis, amelioration of histologic injury, and reduced glomerular permeability and proteinuria [18]. Regulation of autoactivation mechanisms of the complement pathway is maintained by the factors that act in the fluid phase (FH and FI) and factors that are anchored to cell membranes (CR1/CD-35, MCP/CD-46, DAF/CD-55, and protectin CD-59) [19]. Throughout the kidney, the CR1 are expressed only on podocytes [14]. C3GN is not a primary podocytopathy, but podocyte damage with foot process effacement has been reported due to C3 deposition [13, 20]. C3GN develops when the protein regulators of complement activation do not function in the fluid phase, resulting in glomerular deposition of C3b and inactivated C3 by-products (iC3b). We hypothesized that by stabilizing podocytes, remodeling membrane histology, and improving the function of membrane receptors (most notably CR1 activity), repository corticotropin plays a role in clearing glomerular C3 deposits and reducing proteinuria in C3GN.

On our patient's initial presentation and diagnosis of C3GN, he was treated with eculizumab followed by the maintenance repository corticotropin. The patient achieved near-complete resolution of proteinuria within 3 months and stayed in remission for the following 8 months. The patient had a recurrence of proteinuria about 10 weeks after Acthar® was discontinued, which

was again confirmed due to C3GN. Acthar® was reinitiated, and the patient had >50% reduction in proteinuria. The patient was re-treated with eculizumab and achieved complete remission in proteinuria. The patient has stayed in near-complete remission on repository corticotropin (Acthar®) monotherapy for more than a year. We had the option to keep the patient on eculizumab to prevent the recurrence of proteinuria. However, we chose Acthar® for maintenance therapy because of its lower cost and efficacy in reducing proteinuria in nephrotic syndromes of other etiologies [21]. Since C3GN is a complement-mediated disease, eculizumab may be necessary as initial therapy to control the complement dysregulation. However, for maintenance, Acthar® may be adequate to prevent podocytes from any further low complement injury and, consequently, keep patients in proteinuria remission. We believe that Acthar® might also have a role as a maintenance regimen in C3GN in native kidneys, but this needs to be studied further.

In conclusion, this case report suggests that although repository corticotropin may not induce complete remission of proteinuria in C3GN, it may be an effective therapy in reducing proteinuria and maintaining patients in complete remission. Further studies will help us understand the mechanism of action, safety, and efficacy of repository corticotropin (Acthar®) in C3GN.

Statement of Ethics

This case report complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was taken from the patient to use the biopsy images and laboratory data for publication. The institutional review board exempted this case report from the need for approval since it was a retrospective chart review study with no diagnostic or therapeutic interventions involved. The case report does not contain any patient information that can lead to the identification of the patient.

Conflict of Interest Statement

N.S. serves as the speaker bureau for Mallinckrodt Pharmaceuticals, Veloxis, Transplant Genomics, and CareDx. He also has grant/research support as a Principal Investigator on studies from CareDx and Transplant Genomics. M.S.N. and A.S. declare no conflicts of interest.

Funding Sources

The authors have no relevant financial disclosures.

Author Contributions

M.S.N. collected the patient information and clinical data, wrote the first draft, and revised the manuscript for the final submission. A.S. assisted in revising the manuscript. N.S. analyzed the manuscript critically for important intellectual content, suggested revisions, and approved the final manuscript. As the corresponding author, N.S. submitted the final manuscript.

Data Availability Statement

Research data are not shared due to privacy or ethical restrictions.

References

1 Medjeral-Thomas NR, O'Shaughnessy MM, O'Regan JA, Traynor C, Flanagan M, Wong L, et al. C3 glomerulopathy: clinicopathologic features and predictors of outcome. Clin J Am Soc Nephrol. 2019;9(1):46–53.

2 Meri S. Alternative pathway of complement. In: Ratcliffe MJH, editor. Encyclopedia of immunobiology. 1st ed. Academic Press; 2016. p. 325–31.

3 Nester CM, Smith RJ. Diagnosis and treatment of C3 glomerulopathy. Clin Nephrol. 2013;80(6):395–403.

4 Servais A, Noël LH, Roumenina LT, Le Quintrec M, Ngo S, Dragon-Durey MA, et al. Acquired and genetic complement abnormalities play a critical role in dense deposit disease and other C3 glomerulopathies. Kidney Int. 2012;82:454–64.

5 Abbas F, Kossi ME, Jin JK, Sharma A, Halawa A. De novo glomerular disease after renal transplantation: how is it different from recurrent glomerular disease? World J Transplant. 2017;7(6):285–300.

6 Sahin H, Gok Oguz E, Akoglu H, Atilgan G, Ulusal Okyay G, Karaveli Gursoy G, et al. Successful treatment of posttransplant recurrent complement C3 glomerulopathy with eculizumab. Iran J Kidney Dis. 2018;12:315–8.

7 Welte T, Arnold F, Kappes J, Seidl M, Häffner K, Bergmann C, et al. Treating C3 glomerulopathy with eculizumab. BMC Nephrol. 2018;19:7.

8 Le Quintrec M, Lapeyraque AL, Lionet A, Sellier-Leclerc AL, Delmas Y, Baudouin V, et al. Patterns of clinical response to eculizumab in patients with C3 glomerulopathy. Am J Kidney Dis. 2018 Jul;72(1):84–92.

9 Bomback AS, Smith RJ, Barile GR, Zhang Y, Heher EC, Herlitz L, et al. Eculizumab for dense deposit disease and C3 glomerulonephritis. Clin J Am Soc Nephrol. 2012;7:748–56.

10 H.P. Acthar® gel (repository corticotropin injection) [prescribing information]. Hazelwood, MO: Mallinckrodt ARD Inc.; 2015.

11 Hladunewich MA, Cattran D, Beck LH, Odutayo A, Sethi S, Ayalon R, et al. A pilot study to determine the dose and effectiveness of adrenocorticotrophic hormone (H.P. Acthar® Gel) in nephrotic syndrome due to idiopathic membranous nephropathy. Nephrol Dial Transplant. 2014;29(8):1570–7.

12 Markell M, Brar A, Bhela S, Patel A, Salifu M. Use of repository corticotropin (Acthar®) in progressive nephrotic syndrome secondary to transplant glomerulopathy: a report of three cases. Kidney Med. 2019;1(1):31–5.
13 Duineveld C, Steenbergen EJ, Bomback AS, Van De Kar NCAJ, Wetzels JFM. Treatment-resistant nephrotic syndrome in dense deposit disease: complement-mediated glomerular capillary wall injury? Pediatr Nephrol. 2020; 35(9):1791–5.
14 Fearon DT. Human complement receptors for C3b (CR1) and C3d (CR2). J Invest Dermatol. 1985;85:53s–57s.
15 Gong R. The renaissance of corticotropin therapy in proteinuric nephropathies. Nat Rev Nephrol. 2011;8(2):122–8.
16 Bergwall L, Wallentin H, Elvin J, Liu P, Boi R, Sihlbom C, et al. Amplification of the melanocortin-1 receptor in nephrotic syndrome identifies a target for podocyte cytoskeleton stabilization. Sci Rep. 2018;8:15731.
17 Lindskog A, Ebefors K, Johansson ME, Stefánsson B, Granqvist A, Arnadottir M, et al. Melanocortin 1 receptor agonists reduce proteinuria. J Am Soc Nephrol. 2010;21(8):1290–8.
18 Gong R. Leveraging melanocortin pathways to treat glomerular diseases. Adv Chronic Kidney Dis. 2014;21(2):134–51.
19 Salvadori M, Bertoni E. Complement related kidney diseases: recurrence after transplantation. World J Transplant. 2016 Dec 24;6(4): 632–45.
20 Chauvet S, Roumenina LT, Bruneau S, Marinozzi MC, Rybkine T, Schramm EC, et al. A familial C3GN secondary to defective C3 regulation by complement receptor 1 and complement factor H. J Am Soc Nephrol. 2016; 27(6):1665–77.
21 Madan A, Mijovic-Das S, Stankovic A, Teehan G, Milward AS, Khastgir A. Acthar gel in the treatment of nephrotic syndrome: a multicenter retrospective case series. BMC Nephrol. 2016;17:37.