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Case Report

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A case report of atypical hemolytic-uremic syndrome treatment with the first Russian eculizumab in adult patient

Summary

Atypical hemolytic uremic syndrome (aHUS) is a chronic genetically-mediated systemic disease caused by uncontrolled activation of the alternative complement pathway that leads to generalized thrombosis of the microcirculatory vessels (complement-mediated thrombotic microangiopathy, TMA). Plasma therapy was long considered the first-line treatment of aHUS. In the early 2000s, considerable progress in the understanding of aHUS pathophysiology and its treatment was achieved, leading to the emergence of innovative therapeutic approaches. An original drug of eculizumab has shown high efficacy in aHUS patients associated with hematological remission, including renal function recovery in some cases.

Study purpose: To assess the efficacy and safety of the first Russian eculizumab biosimilar for the treatment of aHUS in adults.

Patients and methods: A clinical observation of one adult patient with aHUS was held.

Results: A 46-year-old patient has a history of hypertension since 2012 and maximum BP of 230/130 mm Hg. In 2016, newly diagnosed azotemia was identified (blood creatinine —140 µmol/L, GFR by EPI—54 mL/min/1.73 m^2). In 2018, the patient suffered an acute cerebrovascular accident in the vertebrobasilar area. On the date of admission to the Almazov National Medical Research Center the blood test showed: creatinine —60 µmol/L (GFR by EPI —28 mL/min/1.73 m2), urea —11.52 mmol/L, LDH—130 U/L, complement system C3—1.32 g/L, C4—0.37 g/L, haemoglobin—144 g/L, platelets—302*109/L; urinalysis showed: daily protein loss—2.6 g/day, RBC—0–1 per HPF. Taking into account the kidney damage, the renal fine-needle aspiration biopsy was performed, revealing histopathological findings typical of chronic thrombotic microangiopathy, arteriolar arteriosclerosis of extreme severity with total or subtotal luminal occlusion, extensive secondary perihilar segmental glomerulosclerosis (27%) and global glomerulosclerosis (55%). According to the study results, the secondary genesis of TMA was ruled out, as well as STEC-HUS and thrombotic thrombocytopenic purpura (TTP), systemic diseases (systemic lupus erythematosus, antiphospholipid syndrome (APS), and systemic sclerosis), malignancies, HIV infection, sepsis, malignant hypertension, adverse drug events, or disseminated intravascular coagulation (DIC). Plasma ADAMTS13 levels were also assessed. Its activity was 64% (normal range 93–113%) of ADAMTS13 activity in the control plasma, thus the diagnosis of thrombocytopenic purpura was ruled out. Due to the absence of anti-CFH-antibodies, the antibody origin of aHUS was also ruled out.

To assess the contribution of additional factors promoting the development of TMA, the polymorphism of haemostasis genes was studied to reveal homozygous genotypes of platelet collagen receptors (ITGA2: 807 C/E), heterozygous genotypes of fibrinogen genes (FGB: 455 G/A), folate cycle enzymes (methylenetetrahydrofolate reductase (MTHFR: 677 C/T), methionine synthase (MTR: 2756 A/G (D919G)), responsible for a pronounced tendency towards hyperhomocysteinemia. In the clinical case the diagnosis of aHUS was obvious, which was supported by the classical symptom cluster of TMA and histopathological verification in the absence of data suggestive of other pathological conditions. The peculiarity of this clinical case is the late diagnosis, long-standing course, and severity (complications such as an acute cerebrovascular accident in the vertebrobasilar area, target lesions, kidneys in particular). Taking into account the primary diagnosis, treatment with a standard dose of eculizumab was initiated. After three months of treatment, the patient was switched to therapy with the first Russian eculizumab biosimilar. After the switch from the original drug, the therapy with the biosimilar continued a positive trend including a gradual decline in azotemia level (blood creatinine—115 µmol/L (GFR by EPI—65 mL/min/1.73 m^2), blood urea—6.90 mmol/L), proteinuria (daily protein loss—0.6 g/day). BP was also normalized. No adverse events associated with the therapy were observed.

Conclusion: Based on the evidence obtained, the first Russian eculizumab demonstrated its high efficacy and safety for the treatment of an adult patient with aHUS.

Keywords: diagnosis, long-standing course, segmental glomerulosclerosis, global glomerulosclerosis, vertebrobasilar area, target lesions, kidneys

Volume 8 Issue 2 - 2020

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Received: February 20, 2020 | **Published:** March 19, 2020

Abbreviations: aHUS, atypical hemolytic uremic syndrome; TTP, thrombocytopenic purpura; APS, antiphospholipid syndrome; DIC, disseminated intravascular coagulation; APC, alternative pathway of complement; DPL, decreased daily proteinuria

Introduction

Atypical hemolytic uremic syndrome (aHUS) is an ultra-rare (orphan) genetically-mediated progressive systemic disease from a group of thrombotic microangiopathies (TMA), with poor prognosis. It is caused by uncontrolled complement activation due to genetic mutations of regulatory proteins of the alternative pathway of complement (APC) (CFH, CFI, MCP, THBD) or, less commonly, by antibodies to factor H, the core regulatory protein of the APC. APC activation results in endothelial cell lesions with further generalized thrombogenesis in microcirculatory vessels, the so-called complement-mediated TMA.[1] Platelet surface complement activation, leading to their enhanced functional activity may additionally contribute to the thrombogenesis in patients with CFH mutations. The kidney damage in aHUS seems to be caused by the particular sensitivity of the fenestrated glomerular endothelium to the lesion due to complement regulation disorder.[2] CFH gene mutations are the most common in patients with aHUS (accounting for about 30% of cases). Today over 100 CFH mutations have been identified in pediatric and adult patients with aHUS, including hereditary and sporadic mutations. About 10% of patients with aHUS (mostly children) have mutations in the MCP coding gene. About 10% of patients have CFI mutations. THBD mutations occur in 3–5% of patients. Besides, complement B factor mutations (1–4% of patients) and C3 complement component (2–10% patients), leading to excessive activation, are found in a small share of patients. About 12% of patients with aHUS have mutations in two or more genes of the complement system.[3]

The onset of aHUS is related to the interaction of genetic abnormalities in the complement system with the environmental factors that trigger the additional complement activation in the predisposed patients.[4] The clinical presentation of aHUS is characterized by significant symptom polymorphism. In most cases, the kidney damage manifests itself as acute kidney injury (AKI) with or without oligo/anuria. Proteinuria, sometimes massive, is observed with preserved urine output, to the extent of nephrotic syndrome, particularly with gradual progression of the disease. Haematuria may occur. Of note, AKI is not necessarily the first sign of aHUS. About 17% of patients demonstrate moderate urinary syndrome without renal failure.[5,6] At the onset, the disease may manifest itself as isolated proteinuria with signs of early chronic kidney disease (CKD). Arterial hypertension develops in most patients of any age as an effect of volume overload in patients with oligo/anuria and/or hyperreninemia driven by TMA-associated renal tissue ischaemia. Generalized TMA in aHUS leads to extrarenal signs, including microcirculatory lesions of other organs and systems, including the brain, heart, lungs and gastrointestinal tract. Extrarenal manifestations are observed in 20% of patients, with over two-thirds having multiple extrarenal signs.

aHUS is a diagnosis of exclusion. It is based on characteristic clinical presentation and must be confirmed by laboratory data to exclude other TMAs. As TMAs are characterized by similar clinical and laboratory manifestations and histological findings, irrespective of pathogenesis, it is particularly important to differentiate between the main forms of primary TMA— thrombotic thrombocytopenic purpura (TTP), STEC-HUS and aHUS. In adult patients with TMA major disorders and conditions that can be associated with secondary TMAs are to be excluded, such as those primarily associated with pregnancy and delivery, systemic disorders (SLE, APS, systemic sclerosis), malignancies, HIV infection, sepsis, malignant hypertension, drug therapy, DIC syndrome. Thereby aHUS diagnostics consists of two stages. First, the diagnosis of TMA is to be established, and then a differentiation should be made between primary and secondary TMAs with primary TMAs further differentiated (TTP, STEC-HUS and aHUS). ADAMTS13 activity needs to be tested to exclude TTP in all patients with TMA. The ADAMTS13 activity may be low in patients with aHUS, but it is always above 10%. The exclusion of STEC-HUS and TTP in patients with established TMA will help diagnose the aHUS`. No genetic tests are needed to establish aHUS, and no such tests are considered in the choice of treatment tactics. However, genetic tests are needed for the kidney transplant prognosis, if considered appropriate; in familial aHUS and in patients with relapsed disease. The prognosis in aHUS is very poor, with a high risk of a lethal outcome, and most patients whatever the primary clinical signs, develop the end-stage renal disease (ESRD) and disease relapses.[7]

Plasma therapy was long considered the first-line treatment for aHUS. At the close of the 20th century, significant progress was made in the understanding of aHUS pathophysiology and treatment, leading to development of new drugs with therapeutic effects on the complement system. In 2007 a complement-inhibiting agent eculizumab was developed, which is a recombinant humanised monoclonal antibody binding to human complement protein C5 and inhibiting the activation of the complement-mediated cell lysis. Original eculizumab demonstrated high efficacy both in children and in adults with aHUS, who achieved a haematological remission, improvement and in some cases a complete recovery of the renal function.[8–10] The high cost of the product significantly limited access to the drug in clinical practice for all patients with aHUS who needed it. Since 2019 the first Russian eculizumab biosimilar (Elizaria®, GENERIUM JSC) is available in clinical practice. It demonstrated similar effectiveness and safety versus the original drug in non-clinical and clinical studies, meeting the international regulatory requirements.[11] The results of the phase III clinical trial confirm that proposed biosimilar Elizaria® is comparable to the reference product Soliris® in term of efficacy, safety, immunogenicity and PK/PD parameters in the treatment of paroxysmal nocturnal hemoglobinuria.[12] Marketing authorisation of the first Russian eculizumab led to a 25% cost saving for treatment improving access to the treatment for all patients with aHUS.[13,14] This paper is a case study providing a clear demonstration of successful experience with the Russian eculizumab biosimilar in adult patients with aHUS.

Clinical case

A 46-year-old patient has a history of hypertension since 2012 and maximum BP of 230/130 mm Hg. In 2016, newly diagnosed azotemia was identified (blood creatinine—140 μmol/L). In 2018, the patient suffered an acute cerebrovascular accident (ACVA) in the vertebrobasilar area (VBA). On the date of admission to the FSBI NMRC named after V.A. Almazov the blood test showed: creatinine—260 μmol/L (GFR by EPI—28 mL/min/1.73 m^2), urea—11.52 mmol/L, LDH —130 U/L, complement system C3—1.32 g/L, C4—0.37 g/L, haemoglobin—144 g/L, platelets—302*10^9/L; urinalysis showed: daily protein loss—2.6 g/day, RBC—0–1 per HPF. Taking into account the kidney damage, the renal fine-needle aspiration biopsy was performed. The light-optical study on paraffin sections using the following stains: hematoxylin-eosin, PAS-reaction, Masson's trichrome, Johns's argentation. The renal biopsy sample

Citation: Lavrishcheva IV, Jakovenko AA, Kudlay DA3. A case report of atypical hemolytic-uremic syndrome treatment with the first Russian eculizumab in adult patient. *Urol Nephrol Open Access J.* 2020;8(2):37–40. DOI: 10.15406/unoaj.2020.08.00272

contained cortical and medullary renal tissues; 22 glomeruli (LM-15; IF-7), including 12 (55%) fully sclerosed glomeruli (LM-9, IF-3). The unimpaired glomeruli were significantly enlarged, with a single-loop microvascular wall; with diffuse minimal extension of mesangium; no signs of mesangial and endocapillary hypercellularity, no crescents were observed. The glomerular basal membrane (GBM) was not visually thickened; it was evenly argentated. In the vascular pole area 6 (27%) glomeruli (LM-4, IF-2) were visualised, with extensive secondary perihilar segmented sclerosis with significant podocyte hypertrophy; with isolated foam cells in the lumens of the capillaries involved; with severe insudate changes and rough adhesion to the glomerular capsule; associated with perifocal mesangiolysis.

Multifocal acute tubular epithelium lesion with brush border loss, sharp flattening and significant cell degeneration. Tubular lumens were patent; no casts. Diffuse moderate-grade tubulointerstitial inflammation. Signs of significant tubulointerstitial fibrosis, not otherwise defined, due to small scattered fragments of the cortical layer. Arteriolar and small arterial walls were significantly thickened due to muscle layer hypertrophy, laminated circular subendothelial sclerosis, and circulatory transmural insudative changes; with total and subtotal obturation of the vessel lumen. Medium arterial walls were significantly thickened due to significant intimal fibrosis with subtotal obturation of the vessel lumen. Immunofluerescent investigation was performed in cryostat sections by the direct method using FITC conjugated anti-human IgA, IgG, IgM, C3, C1q, fibrin, kappa and lambda light chain antibodies. Diffuse expression of C3, C4 in the arteriolar and small arterial walls and segmentary glomerulosclerosis sites was observed. The histology characteristic of extremely severe chronic thrombotic microangiopathy; arteriolar-arteriosclerosis with total and subtotal obturation of the vessel lumen; major secondary perihilar segmented glomerulosclerosis (27%); full glomerulosclerosis (55%). According to the study results, the secondary genesis of TMA was ruled out, as well as STEC-HUS and TTP, systemic diseases (SLE, APS, and systemic sclerosis), malignancies, HIV infection, sepsis, malignant hypertension, adverse drug events, or DIC. Plasma ADAMTS13 levels were also assessed. Its activity was 64% (normal range 93–113%) of ADAMTS13 activity in the control plasma, thus the diagnosis of thrombocytopenic purpura was ruled out. Due to the absence of anti-CFH-antibodies, the antibody origin of aHUS was also ruled out.

To assess the contribution of additional factors promoting the development of TMA, the polymorphism of haemostasis genes was studied to reveal homozygous genotypes of platelet collagen receptors (ITGA2: 807 C/E), heterozygous genotypes of fibrinogen genes (FGB: 455 G/A), folate cycle enzymes (methylenetetrahydrofolate reductase (MTHFR: 677 C/T), methionine synthase (MTR: 2756 A/G (D919G)), responsible for a pronounced tendency towards hyperhomocysteinemia. In the clinical case, the diagnosis of aHUS was obvious, which was supported by the classical symptom cluster of TMA and histopathological verification in the absence of data suggestive of other pathological conditions. The peculiarity of this clinical case is the late diagnosis, long-standing course, and severity (complications such as an ACVA in the VBA, target lesions, kidneys in particular). Pathogenetic therapy with the original eculizumab at the standard dose (2 courses) was initiated in May 2019, based on the primary diagnosis. Therapy led to a gradual decrease of the blood creatinine level (blood creatinine prior to therapy was 260 µmol/L, and changed over time to 190 µmol/L), decreased daily proteinuria (DPL) (DPL from 2.6 g/day to 1.8 g/day). In June 2019 the patient has been transferred to the first eculizumab biosimilar therapy. After the switch from the original drug, the therapy with the biosimilar showed a continued positive trend (Figure 1) including a gradual decline in azotemia level (blood creatinine—115 µmol/L (GFR by EPI—65 mL/min/1.73 m^2), blood urea—6.90 mmol/L), proteinuria (daily protein loss—0.6 g/day).

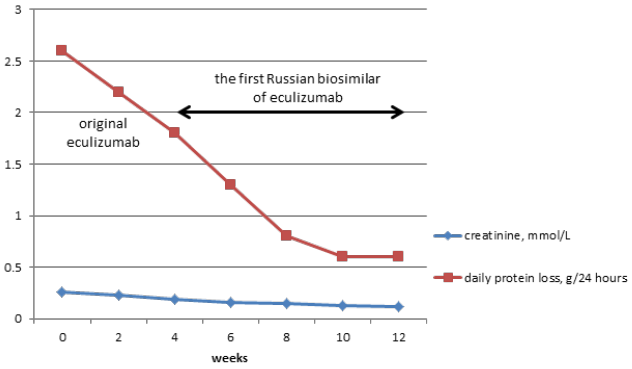

Figure 1 Laboratory results of patient treated with eculizumab over time.

BP was also normalized. No adverse events associated with the therapy were observed. A repeated renal biopsy (after therapy with the first Russian biosimilar) was performed, showing a marked positive trend for arteriolar and small arterial lesions, tubulointerstitial inflammation (according to the light-optical study on paraffin sections using the following stains: hematoxylin-eosin, PAS-reaction, Masson's trichrome, Johns's argentation. The renal biopsy sample contained a cortical and medullary renal tissues; 27 glomeruli (LM-10; IF-17), including 18 (66%) fully sclerosed glomeruli (LM-6, IF-12). Glomeruli were significantly enlarged; with a single-loop microvascular wall; no signs of mesangial and endocapillary hypercellularity, no crescents were observed. GBM is not visually thickened; single-loop, evenly argentated. In 2 (7%) of glomeruli (LM-1, IF-1) secondary segmented glomerulosclerosis with insudative changes was observed. Tubular epithelial cytoplasm was granular, focal acute lesion of the tubular epithelium was observed with partial loss of the brush border. Tubular lumens were patent; no casts. Minor tubular atrophy with thickening and shrinking of the tubular basal membrane (20%) was observed. Mild interstitial fibrosis (20%). Focal moderate medullary small vessel endotheliosis—hyperchromia and hypertrophy of vessels, swollen ample cytoplasm. Arteriolar and small arterial walls were significantly thickened due to muscle layer hypertrophy; focal insignificant insudative changes; focal moderate subendothelial oedema was observed.

Medium arterial walls were significantly thickened due to significant intimal fibrosis with sharp narrowing of the vessel lumen. An immunofluorescent investigation was performed in cryostat sections by the direct method using FITC conjugated anti-human IgA, IgG, IgM, C1q, C3, fibrinogen, kappa and lambda light chain antibodies. The results were negative with all reagents. Chronic and residual focal acute microangiopathic renal tissue abnormalities: focal moderate medullary small vessel endotheliosis; focal moderate subendothelial arteriolar and small arterial wall oedema; significant medium-sized arterial wall sclerosis with sharp narrowing of vascular lumen; significant vicarial glomerulomegaly, complete (66%) and secondary segmented (7%) glomerulosclerosis; acute focal tubular epithelial lesion; minor tubulointerstitial fibrosis (20%); no arteriolosclerosis.

Discussion

Today eculizumab is considered the most effective and pathogenetically justified method of treatment of aHUS in adult patients. Structurally eculizumab is a recombinant humanized monoclonal antibody, kappa immunoglobulin (IgG2/4k), which binds to the C5 human complement protein and inhibits the activation of complement-mediated cell lysis. The antibody consists of human Ig constant regions and complementary deterministic mouse immunoglobulin regions embedded in the light and heavy chain variable regions of the human antibody. The composition of eculizumab includes two heavy chains (448 amino acids each) and two light chains (214 amino acids each). The molecular weight is 147,870 Da. Eculizumab is produced in NS0 mouse myeloma cell culture and undergoes purification by affine and ion-exchange chromatography. Specific virus inactivation and removal are also part of the substance manufacture process. The mechanism of action of eculizumab also involves inhibition of the activity of the terminal complex of the human complement, with a high affinity to its C5 component. As a result, the cleavage of C5 component into C5a and C5b and the formation of the C5b-9 complement terminal complex are completely blocked. Thereby eculizumab prevents excessive activation of the terminal complement complex in patients with atypical hemolytic uremic syndrome (aHUS). The first Russian eculizumab biosimilar demonstrated high efficacy in this case study, leading to a significant improvement of the renal function, relief of proteinuria, normal BP. It is of note that no significant adverse events potentially associated with eculizumab were observed during the entire follow-up period. No adverse reactions requiring treatment interruption or discontinuation were observed in the patient during the treatment period.

Conclusion

This clinical case provides an objective demonstration of high efficacy and safety of the first Russian eculizumab biosimilar used for therapy in an adult patient with aHUS. Therapy with the first Russian eculizumab helped the patient rapidly achieve a stable clinical and laboratory remission, contributing to a positive prognosis for renal function recovery, as evidenced by histological study (improvement of arteriolar and small arterial lesions, and of tubulointerstitial inflammation).

Acknowledgments

None.

Conflicts of interest

The author declares there is no conflict of interest.

Funding

None.

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