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The use of belatacept[1] in kidney transplantation

N.N. Babenko, V.A. Goryainov, M.M. Kaabak,

V.V. Nikoda, E.A. Lishova

Petrovsky National Research Centre of Surgery,

2 Abrikosovsky Ln., Moscow 119991 Russia

Correspondence to: Mikhail M. Kaabak, Prof., Dr. Med. Sci., Head of Department of Kidney Transplantation at Petrovsky National Research Centre of Surgery, e-mail: kaabak@hotmail.com

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Background: *kidney transplantation efficacy is limited by immunosuppression nephrotoxicity, antibody-mediated and chronic rejection. Avoiding immunosuppression nephrotoxicity is a promising strategy to improve long term outcomes. Belatacept, a synthetic immunoglobulin which blocks CD28-B7 pathway of T-lymphocyte costimulation, is considered as an alternative to calcineurin inhibitors in maintenance immunosuppression since it has no nephrotoxicity.*

Purpose. *To evaluate belatacept efficacy and safety for maintenance immunosuppression therapy after kidney transplantation based on the clinical experience.*

Material and methods. *From March 2017 to May 2018, we used belatacept in five kidney transplant recipients (one female and four males*

[1] Belatacept. State Registry of Medicines. Registration number LP-001667. Electronic resource: http://grls.rosminzdrav.ru/grls.aspx

aged from 4 to 21 years) in the Kidney Transplantation Department of Petrovsky National Research Centre of Surgery Three kidneys were taken from related living donors, two kidney grafts were from deceased donors. Conversion from CNI to belatacept was performed between 6 and 112 months after transplantation. Patients were followed-up for average 12 months after conversion. We have described here these five cases, providing individual indications and the outcome of conversion.

Results. *The conversion failed in two children switched to belatacept with the purpose to improve compliance. Three patients switched to belatacept because of tacrolimus toxicity demonstrated good results in one year follow up.*

Conclusion. *Belatacept demonstrated good results if was used instead of calcineurin inhibitors when the latter were poorly tolerated. The use of belatacept in multidrug immunosuppression in noncompliant patients was ineffective.*

Keywords: kidney transplantation, immunosuppression, belatacept

CKAT, cadaveric kidney allotransplantation

CMV, cytomegalovirus

CRF, chronic renal failure

EBV, Epstein-Barr virus

IFTA, Interstitial Fibrosis and Tubular Atrophy

IS, - immunosuppression

KAT, kidney allotransplantation

MMF, mycophenolate mofetil

NAB, needle allograft biopsy

PCS, pyelocaliceal system

US, ultrasonography

VUR, vesicoureteral reflux

The efficacy of kidney allotransplantation (KAT) is limited by immunosuppresion nephrotoxicity, and also by humoral and chronic rejection [1]. The development of immunosuppressants with minimal nephrotoxic effect is crusial for improving the results of kidney engraftment. With the improved understanding of rejection molecular mechanisms, some promising components to prevent acute or chronic rejection are under development or have already been developed. However, these new molecules must be evaluated for their efficacy and safety to ensure that they do not increase the risk of developing infectious complications and do not contribute to tumor formation in the renal allograft, on the one hand, and effectively prevent rejection, on the other.

Belatacept (LEA29Y), a new drug blocking the CD28-B7 pathway, is one of such agents, which has been developed as an alternative to calcineurin inhibitors (Figure). There are 2 components identified in ligand B7: B7-1 or CD80, and B7-2 or CD86. Belatacept is a modified molecule of CTLA4-lg, which prevents the secondary activation of the T-lymphocyte signal, thus causing CD 28-80/86 blockade. A lot of reports on studying this agent have been published, presenting, however, contradictory opinions [2-7]. That is why we decided to describe our clinical experience.

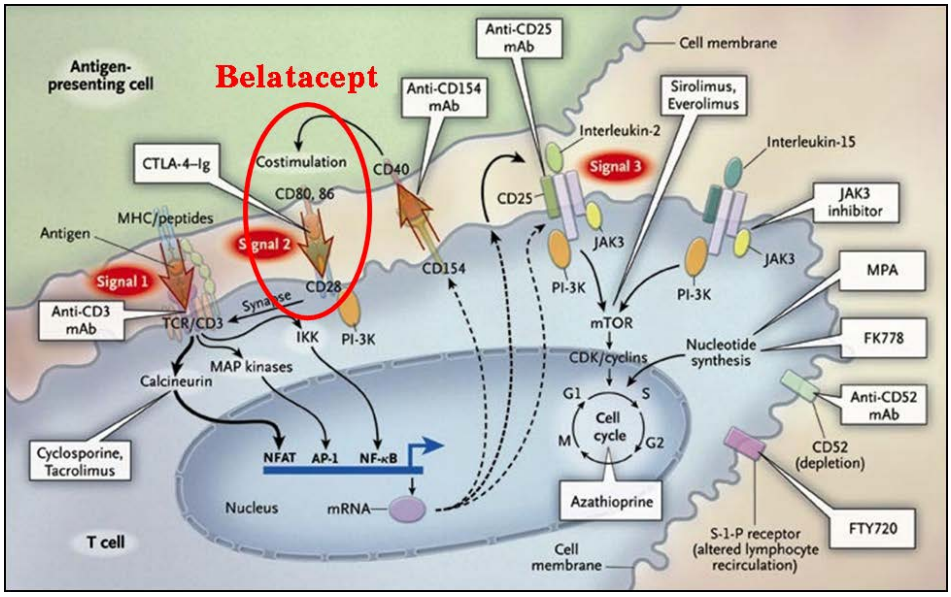

Figure. Schematic representation of the mechanisms of action of belatacept and other immunosuppressants. Adapted from "Early Conversion to Belatacept in Patients with Presumed Calcineurin Inhibitor Nephrotoxicity". Luz Liriano-Ward, Ron Shapiro, Vinay Nair. TTS Congress 2016, Hong Kong

Material and methods

A group of 5 patients (children and adolescents) aged 4 to 21 years (4 male and 1 female) was formed in March 2017 for conversion from tacrolimus to belatacept. The conversion was undertaken at the time from 6 to 112 months after transplantation. The belatacept dose was 10 mg/kg at 4 initial dosings: on day 0, day +4, day +14, day +28; later on, 10 mg/kg were administered once every 4 weeks for 4-5 months. From the 16-20th week, the dose of belatacept was reduced to 5 mg/kg administered every 4^{th} week.

In 2 patients, the intervals between belatacept administrations were subsequently increased to 8 weeks due to clinical manifestations of hyperimmunosuppression. Tacrolimus was canceled at 0-7 week after the

start of belatacept administration. Indications for conversion from tacrolimus to belatacept included: tacrolimus adverse side effects (nephrotoxicity, hepatotoxicity, diarrhea, diabetogenicity) in 2 patients; unsatisfactory compliance in 2 patients; immune toxicity of tacrolimus in the form of hyperimmunosuppression syndrome in 1 patient. Before the conversion, the presence of anti-EBV was confirmed by laboratory tests in all 5 patients. The description of clinical cases is followed below.

Case 1

Patient MK, born in 1996. Diagnosis: "Nephropathic cystinosis; end-stage chronic renal disease (CRD); preemptive kidney transplantation from the mother on 24.11.2008; diabetes mellitus from 2011 to 2017".

The renal dysfunction manifested itself in the form of proteinuria emerged at the age of one-year-old age. At 7 years of age, based on nephrobiopsy results and the ophthalmologist's examination showing the deposition of cystine crystals in the cornea, the diagnosis of "cystinosis" was made.

Preemptive kidney transplantation from the mother was performed on 24.11.2008. The induction therapy with alemtuzumab was administered. He had an immediate graft function. The blood level decreased below 3 mg% on the 1st day. Maintenance immunosuppression (IS) included: tacrolimus from day 0, combination with mycophenolate mofetil (MFF) and prednisolone from day 4, with the withdrawal of the latter 2 days later. The blood creatinine was about 80-100 μmol/L until October 2009, when its increase to 120 μmol/L was noted. The planned needle allograft biopsy (NAB) revealed a mild tubulitis for which the MMF dose was increased. Over time, the creatinine level was increasing. The NAB in October 2011, demonstrated the

increasingly pronounced morphological signs of rejection, which served the reason for conducting pulse therapy combined with steroid recycle therapy. Alongside with the above, the development of diabetes mellitus de novo was marked; insulin was prescribed. A rapid reduction of the prednisolone dose and its withdrawal in October 2014 failed to cope with the diabetes. From 2012 to 2016, the dose of MMF was lower than the calculated one because of diarrhea. The graft function remained stable: blood creatinine of 150-140 μmol/L, proteinuria about 100 mg/day. The control NAB in April 2014 showed positive dynamics. The control biopsy in March 2017 revealed the progression of Interstitial Fibrosis and Tubular Atrophy (IFTA), which in the absence of tubulitis was regarded as a manifestation of tacrolimus nephrotoxicity. Given three side effects of tacrolimus, i.e. diabetes, nephrotoxicity, and diarrhea, a conversion to belatacept was initiated from March 21, 2017: 600 mg at day 0, day +4, day +14 and day +28; 650 mg at day +56 and at day +84; further, 350 mg every 4th week, intravenously. Tacrolimus was canceled on May 16, 2017, insulin was withdrawn on October 15, 2017.

At the latest examination on May 15, 2018, the patient's height was 165 cm, the body weight was 62 kg, blood creatinine was 137 μmol/L, proteinuria 236 mg/day, fasting blood glucose 4.2 mmol/L, glycated hemoglobin 6%. IS included: belatacept, 300 mg once per 4 weeks; MMF, 1250 mg/day, intravenously. Intravenous infusions of cystagon, 1200 mg/day, were used for the treatment of the underlying disease (Table 1, 2).

Table 1. Patient MK, changes in laboratory parameters and immunosuppression over time

Date, years			2008	2011	2012 – 2013	2014– 2015	2016	March 2017	May 2017	October 2017	December 2017	May 2018
Blood creatinine, μmol/L			87	211	148	150	141	135	149	133	139	137
Proteinuria, mg/day			85	149	138				82	149	152	236
Glycohemoglobin			6h	7	6.8	6.6	6.5	6.7	6.2.	5.6	6.5	6.5
Insulin dose, U/day					20	30	20	10	6	4	0	0
Immunosuppression	tacrolimus	mg/day	6th	5	4	3	3	3	Cancelled on 16.05.2012			
		ng/ml	6.2	8.4	9.1	4.3	5.1	3.6				
	MMF, mg/day		500	1000	540	180	180	500	750	1250	1250	1250
	belatacept, mg							600	600	300	300	300
	steroids, mg		0	25 Pulse therapy 625mg 3 times per day	2.5	Cancelled on 24.10.2014						

Table 2. Patient MK, needle allograft biopsy (NAB), Banff classification semi-quantitative scoring

date	t	v	i	g	ah	ct	ci	cv	cg	mm	ptc	CADi	Conclusion
22.12.2008	0	0	0	0	0	0	0	0	0	0		0	Normal
23.10.2009	0.5	0	0.5	0	0	1	1	0	0	0		2.5	Borderline alterations
31.10.2011	1	0	0.5	1	0	1	1	0	0.1	0		2.6	Slightly pronounced signs grade 1 acute cellular rejection are somewhat

													more active than borderline alterations Suspected initial manifestations of mildly expressed chronic rejection with segmental glomerulitis.
18.04.2014	0.3	0	0.5	0	0	0.5	0.5	0	0	0	0	1.5	Borderline slightly pronounced alterations, hyalinosis of individual glomeruli
14.03.2012	0	0	0	0	1	2	2	0	0.5	1	0	5.5	Glomerular hyalinosis; grade 2 parenchyma sclerosis and atrophy; grade 1 arteriolar segmental hyalinosis. No rejection

Case 2

Patient TE, born in 2012. Diagnosis: "Infantile nephrotic syndrome, end-stage chronic renal disease (dialysis since 09.06.2014, cadaveric kidney allotransplantation (CKAT) on 16.11.2014, with allograft functioning until 09.01.2015, repeated CKAT on 27.09.2016).

Urinalysis made at the age of 1 month showed no abnormalities; after acute respiratory disease at 4 months old, proteinuria of 2 g/L occurred. In

April 2014, the blood creatinine was 185-158 μmol/L. The dialysis was started on urgent indications on 09.06.2014, the blood creatinine level being 1123 μmol/L. In CKAT No.1, the induction IS included Campath® in combination with Soliris®; the maintenance IS included Prograf® in combination with Myfortic® The primary graft function was satisfactory: blood creatinine established at about 25 μmol/L from day 1 after surgery, proteinuria was below 100 mg/day. On December 23, 2014, respiratory viral infection occurred accompanied by febrile temperature and graft dysfunction, which led to a rapid functional loss on 09.01.2015. The transplant was removed on 15.01.2015. The peritoneal dialysis was initiated that was complicated by peritonitis in summer 2015. In CKAT No. 2: the induction IS included Campath® in a combination with Soliris®, the maintenance IS with tacrolimus in a combination with MMF. The primary graft function was satisfactory: 2190 ml of urine excreted on the 1st day, azotemia normalized on day 2; blood creatinine at discharge was 63 mmol/L, albumin-creatinine index was 18.8. After discharge, there was an irregular intake of tacrolimus and steroids. At a month after CKAT the patient was febrile, had oliguria, a 3-fold blood creatinine increase, weight gain. Four hemodialysis sessions were performed. NAB demonstrated grade 2b acute cellular rejection. There was no effect from the administration of solu-medrol, Campath, and steroid recycle therapy. The cascade of plasmapheresis (total 3 sessions) and thymoglobulin therapy were initiated. The diuresis was restored on day 22; a slow decrease of nitrogenous waste products in blood was noted. There was a relapse of fever on 05.12.2016, decreased diuresis, increased blood creatinine. IS was increased (with the increased dose of MMF, the steroid recycle therapy). In March 2017, a conversion from tacrolimus to belatacept was undertaken in order to

improve compliance. In May 2017, while on erythropoietin-beta therapy, the patient developed anemia and agranulocytosis. Intermittently, leukopoiesis was stimulated with Neulastim®, but agranulocytosis recurred from time to time. Body temperature increases to 39° C were recorded 2 times per month from August 2017, 2 times per week from December 2017. On 15.12.2017, pneumonia was diagnosed; Wilprafen® and then Meronem® were administered. From December 2017, the intervals between belatacept dosing were increased to 8 weeks. In January 2018, there was no evidence of infection; blood creatinine was 180 μmol/L, proteinuria being below 100 mg per day. The inability to conduct effective immunosuppression due to infectious complications led to a planned resumption of dialysis in April 2018 at a blood creatinine level of 270 μmol/L (Table 3).

Table 3. Patient TE, NAB, Banff classification semi-quantitative scoring. Changes in immunosuppression

Date, years	t	v	i	g	ah	ct	ci	cv	cg	mm	ptc	CADi	Conclusion
03.11.2016	1	2.5	3	0	0	1	1	0	0	0		5	Grade 2b acute cellular rejection. Association of rejection with viral graft disease could not be excluded
Solu-medrol®, Campath®, steroid recycle therapy, plasmapheresis # 3, thymoglobulin.													
06.03.2017	1	0	0	0	0	0	0	0	1.5	0	0	1.5	Grade 1-2 chronic transplant glomerulopathy as a manifestation of chronic humoral rejection, mild signs of grade 1a acute cellular rejection.
The administration of belatacept®, tacrolimus withdrawal													
27.10.2012	0	0	0	0	0	2	2	1	2	2	0	9	Grade 1 chronic transplant glomerulopathy, stroma sclerosis with tubular atrophy of grade 2 as an outcome of chronic humoral rejection. No evidence of acute rejection

Case 3

Patient BG, born in 2000. The diagnosis read "Reflux-nephropathy, end-stage chronic renal disease (on dialysis from 10.01.2014, CKAT on May 28, 2016)".

On the 1st week of life, there was noted an enlargement of the ureters, and pyelocaliceal system (PCS) on both sides. At the age of 3.5 months, the resection of the distal sections of both ureters was made with their neoimplantation into the bladder, according to Politano-Lidbetter technique. Postoperatively, leukocyturia persisted. At the age of 11 months, the patient underwent bilateral pyelostomy, had a repeated pyelostoma prolapse, no improvement of PCS on ultrasonography (ultrasound). From 1 year of age, there was a gradual deterioration of kidney function. In December 2001, after a regularly prolapsed pyelostoma on the right, a bilateral T-shaped ureterocutaneostomy was performed. There were frequent recurrences of urinary tract infection; a prolonged antibacterial therapy, and the treatment for urosepsis were performed. In February 2005, the distal sections of the left ureter were resected, and its neoimplantation into the bladder, according to Politano-Lidbetter technique, and the closure of the left ureterocutaneoostoma with a flap were performed. In April 2007, the endoscopic modeling of the right ureter mouth and the endoscopic correction of vesicoureteral reflux (VUR) with collagen on the right were made. In April 2010, the endoscopic modeling of the right ureter mouth was performed. In the end of December 2013, acute viral respiratory infection occurred, diuresis decreased; on 10.01.2014 dyspnea, convulsions, and coma 1 developed. Blood test demonstrated creatinine 1870 μmol/L, urea 64.5 mmol/L, anemia (Hb 44 g/L), hyperkalemia (K+ 6.95 mmol/L). Hemodialysis was started immediately. In April 2015, the patient was placed

on the waiting list for cadaveric kidney transplantation in NRCS. The CKAT was performed on May 28, 2016. The graft primary function was satisfactory: day 1 diuresis made 1700 ml; there was a decrease in creatinine to subnormal values on day 1. Induction IS with solu-medrol, further IS with tacrolimus in combination with MMF and prednisolone were given. After discharge, the patient's poor compliance was noted: he often ignored regular tests, did not follow recommendations for taking medications. In October 2016, due to the increased creatinine level, proteinuria, and unstable tacrolimus concentration, NAB was performed showing borderline abnormalities, grade 1 IFTA (t1, v0, i1, g0, ah0, ct1, ci1, cv0, cg1.5, mm1). Daily dosing of prednisolone was continued, IS regimen was optimized by reducing the dosing frequency. From 16.02.2017 and further on, cytomegalovirus (CMV) persisted in blood; valganciclovir therapy was given. From 18.04.2017, tacrolimus was canceled due to poor compliance and the therapy with belatacept was started. The patient came for belatacept administration visits with a delay of 1 -2 weeks. From late October 2017, there was an increased blood creatinine level, proteinuria, a graft enlargement, hematuria. The prednisolone dose was increased but with no improvement. Pulse therapy and an increase in the dose of oral prednisolone did not bring improvement either. NAB on 15.11.2017 detected CMV-associated nephritis. Belatacept was replaced with tacrolimus oral dose of 10 mg per day, valganciclovir was administered at a therapeutic dose; that produced temporary positive changes; the blood tests of 01.12.2017 demonstrated the blood creatinine decrease to 371 μmol/L. At laboratory control tests on May 10, 2013, blood creatinine was 400 μmol/L.

Case 4

Patient EB, born in 2009. The diagnosis read: "End-stage chronic renal disease of unclear etiology (on dialysis from 04.12.2012, KAT from the mother on November 20, 2013). Critical growth retardation, somatotropin administration since September 2015".

The patient had a poor weight gain since birth. At a planned physical examination in September 2011, the ultrasonography revealed an increased size, hyperechogenicity, and the absence of differentiation of the renal parenchyma. By November 2012, the patient had the end-stage CRD, and severe anemia. At the place of residence (in Moldova), four hemodialysis sessions were given. From December 2012, the patient was followed-up in St. Vladimir State Children's Clinical Hospital, where a peritoneal catheter was implanted on 14.12.2012; and on 16.12.2012, the peritoneal dialysis was started. In July 2013, the infection of the peritoneal catheter inlet developed, for which a conservative therapy was performed. In August 2013, the patient had an occlusion of the retina artery of both eyes complicated by a bilateral amaurosis with a subsequent slow recovery of vision.

Induction IS with Campath®; further IS with tacrolimus (Prograf®, and with Advagraf® from 23.01.2014) in combination with Myfortic® were given. There was an immediate graft function, diuresis on day 1 made 1760 ml. The blood subnormal creatinine reduction values were noted on day 0.

The graft function remained satisfactorily stable throughout the postoperative period, the blood creatinine level was 44 μmol/L, proteinuria 0.034 g/L (the protein/creatinine ratio of a single urine sample was 0.09). NAB at 1 month after transplantation showed no rejection. Throughout the postoperative period, the child had recurrent bronchopulmonary infections and recurrent EBV viremia, which required a temporary interruption of IS.

NAB at 1 year after transplantation showed slight borderline abnormalities, C4d+ was detected in the kidney microcirculatory bed. The conversion to sirolimus was undertaken in December 2014 due to persisting EBV. While on that therapy, EBV was not detected in blood, but recurrent bronchopulmonary infections persisted. From March 2015, EBV titer of 10^4-10^5 was occasionally detected in blood again. NAB of 18.11.2016 demonstrated slight borderline abnormalities, IFTA progression (t0.5, i1, ct1, ci1, cg0.5). Given the biopsy results and a stable absence of viruses for 12 months, the patient was converted from sirolimus to tacrolimus in December 2016, which resulted in an almost continuous flow of otolaryngological and bronchopulmonary infections with febrile body temperature. In connection with this, on 11.04.2017, a conversion to belatacept was undertaken with tacrolimus withdrawal in May, 2017. After the conversion, bronchopulmonary infection episodes were noted in December and February 2018; and in February 2018, the rate of administering belatacept was reduced to 1 time per 8 weeks. At the follow-up visit in May 2018, blood creatinine was 56 μmol/L, proteinuria 141 mg/L, the infection status was without complications.

Case 5

Patient KSh, born in 2013. The diagnosis read "Reflux-nephropathy, end-stage chronic renal disease (on hemodialysis from 04.07.2015, KAT from grandmother in May 16, 2016). Congenital liver fibrosis".

The medical history of anemia from birth was noted (Hb 100-110 g/L). At the age of 1 month, she had osteomyelitis, and at the same time she had a spongy kidney. From mother's words, there was no other pathology. From the age of 6 months, the patient suffered from mild skin itch (eyes,

ears), regarded as allergy manifestations, and, therefore, took antihistamines with a partial effect. In April 2015 (at the age of 2 years and 2 months old) she had an acute intestinal infection and was treated on an outpatient basis. In May 2015, hemoglobin decreased to 76 g/L. In June 2015, blood creatinine was 413 μmol/L; on 04.07.2015 hemodialysis was urgently started via a temporary-placed central venous catheter, and dialysis catheters were repeatedly changed.

On May 16, 2016, KAT from the grandmother was performed. Prior to transplantation, the cystography was performed that revealed Grade 4 VUR on both sides, for which the transplantation was supplemented with native bi-nephroureterectomy. An immediate graft function was observed, diuresis on day 1 made 3470 ml; creatinine decreased to normal on day 0. Induction IS with alemtuzumab in combination with eculizumab was performed, further IS included tacrolimus in combination with MMF. In the early postoperative period, the liver function tests gave worsened results showing increased activities of transaminases, alkaline phosphatase and gamma-glutamyltranspeptidase. The intraoperative biopsy of the liver demonstrated the data suggesting the development of liver cirrhosis, most likely due to congenital biliary hypoplasia. With the decrease of tacrolimus dose to the lower protocol limit, a significant positive dynamics was observed in the liver. The tacrolimus concentration established at a level of 2.8-4.8 ng/ml. The blood creatinine was 33-54 μmol/L.

The scheduled tests at a local medical facility on March, 14, 2017, showed an increased creatinine level to 120 mcmol/L, decreased hemoglobin to 81-90 g/L, hyperkalemia (6.5-6.7 mmol/L). From March 30, 2017, the episodes of arterial hypertension, fever, proteinuria growth up to 2 g/L in a single portion of urine were noted. The blood concentration of tacrolimus

was 1.7 ng/ml. The results of NAB of 03.04.2017 suggested chronic transplant glomerulopathy as a manifestation of humoral rejection in combination with grade 1a cellular rejection, C4d deposits in the microcirculatory bed. Pulse therapy with steroids was performed, intravenous immunoglobulin infusions gave a short-term effect in the form of decreased creatinine, but with persisting massive proteinuria. Concurrently, the patient was converted from tacrolimus to belatacept on May 16, 2017, aimed at reducing hepatotoxicity. After the tacrolimus discontinuation, the liver enzymes normalized and proteinuria stabilized. While on belatacept therapy for a year, creatinine decreased to 70 μmol/L, proteinuria stabilized at about 700 mg/day, protein-creatinine index was 0.88.

Discussion

With the advent of belatacept, optimistic expectations were associated with improving the long-term results of kidney transplantation thanks to no drug nephrotoxicity. However, the high incidence of acute rejection episodes and their severity as identified in Phase III clinical trials of the drug in comparion with similar effects of cyclosporine, raised a certain concern. Since the comparison of belatacept with cyclosporine revealed more rejections in the belatacept group, many researchers expected more vivid signs of rejection activation when comparing belatacept with tacrolimus that had proved to be a more potent immunosuppressant than cyclosporine. Therefore, it was not a surprise to see the greater rates and severity of rejection episodes in a randomized controlled trial published by de Graav et al. in March 2017 [8], when comparing belatacept as a basic component of the maintenance IS from the first days after transplantation with tacrolimus.

In addition to the basic component, all patients received the induction IS with basiliximab, and mycophenolate and steroids as the components of the maintenance IS. The incidence of rejection in the group of belatacept was 55% during the first year after transplantation versus 10% in the tacrolimus group. That study did not manage to identify biomarkers that could determine which of the patients could be expected to have a rejection with belatacept treatment.

Therefore, belatacept as the basis of the initial IS regimen is not suitable for most patients, at least after the induction with basiliximab. The reports on belatacept trials with the induction provided with other biological agents have not yet been published.

In addition to being used as a starting IS therapy, belatacept has been used for conversion from calcineurin inhibitors with clinically significant toxicity of the latter [9]. We have also considered the possibility of using belatacept in noncompliant patients to improve the IS efficacy by means of professional-made administered intravenous infusion of a basic immunosuppressant at a rate of once per every few weeks. We esteemed belatacept as an additional tool to further improve the kidney transplantation outcomes, besides to the original surgical technologies [10, 11], methods to correct reperfusion injury [12, 13], and IS [14, 15].

Our experience is small in sample size: there were only 5 patients who received belatacept for 1 year. However, for lack of other experience in Russia, we consider it important to inform the professional community about the results we have obtained. In addition, the expiry of the belatacept authorization in Russia in April 2017 requires physicians to make extraordinary efforts to prescribe the drug to patients. Therefore, a

description of the advantages and disadvantages of belatacept even in a small number of patients is necessary for the Russian transplant community.

We became convinced of the efficacy of belatacept as an alternative to tacrolimus in the patients we observed who had various manifestations of tacrolimus toxicity.

Patient MK, a young man with diabetes mellitus that developed while on a many-year therapy with tacrolimus after the treatment of the renal graft rejection with steroids demonstrated the recovery of carbohydrate metabolism autonomous regulation at 7 months after tacrolimus discontinuation. Within a year after that discontinuation, the function of the renal graft function remained satisfactory, there was no activation of the rejection reaction.

Patient KSh, a 3-year-old girl, experienced a marked intolerance to tacrolimus because of the concomitant liver fibrosis associated with the underlying disease. The conversion to belatacept enabled to normalize the liver enzyme activities and the child's health status, and also to establish the control over the detected humoral rejection shortly before the conversion. It is likely that with good tolerance of tacrolimus, the rejection in this patient could be cured with conventional therapy; however, the congenital liver fibrosis did not allow the child to be treated with normal or elevated doses of tacrolimus, which contributed to the rejection progression. Belatacept in that patient became an indispensable alternative.

Patient EB, a 4-year-old boy, suffered from immune toxicity of tacrolimus post-transplantation, which manifested itself as respiratory tract infections. Conversion to a proliferative signal inhibitor led to an improvement in the course of bronchopulmonary infections, but was accompanied by the intensified rejection process. The return to tacrolimus

led to an increased respiratory tract infection. It was belatacept that helped to break this vicious circle; the treatment with belatacept for a year allowed an effective control of both the rejection and the infectious process.

Two patients with confirmed non-compliance, a boy of 4 years and a teenager of 16 years, did not benefit from the belatacept administration. If belatacept had been the only component of the maintenance IS, then its administration under the physician supervision would have allowed for the implementation of an effective IS. Since the IS in those children was multi-component, the identified non-compliance continued to have a negative impact on the graft function, despite the treatment with belatacept. Of course, it is difficult to imagine a patient with proven non-compliance on CNI monotherapy in real clinical practice, since incompetence is usually detected as a result of the activated rejection that is accompanied by the administration of additional IS components. Therefore, we do not think that non-compliance should be considered as an indication for switching to belatacept.

Conclusions

1. Belatacept is a valuable component in the arsenal of immunosuppressive drugs used in organ transplantation.
2. Belatacept has shown good results when used instead of calcineurin inhibitors with poor tolerance of the latter.
3. The use of belatacept in the multicomponent immunosuppression in noncompliant patients gives no expected effect.

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