DOI:10.23873/2074-0506-2019-11-1-21-36

Multipotent mesenchymal stem cells in renal transplantation

N.V. Borovkova[1], M.Sh. Khubutiya[1], O.N. Rzhevskaya[1],

A.V. Pinchuk[1], D.A. Vasil'chenkov[2]

[1]N.V. Sklifosovsky Research Institute for Emergency Medicine,

3 Bolshaya Sukharevskaya Sq., Moscow 129090 Russia;

A.I. Yevdokimov Moscow State University of Medicine and Dentistry,

1 Bldg. 20 Delegatskaya St., Moscow 127473 Russia

Correspondence to: Olga N. Rzhevskaya, Dr. Med. Sci., Leading Researcher of the Kidney and Pancreas Transplantation Department, N.V.Sklifosovsky Research Institute for Emergency Medicine,

e-mail: dr_rzhevskayaolga@mail.ru

Received: December 18, 2018

Accepted for publication: January 15, 2019

Borovkova N.V., Khubutiya M.Sh., Rzhevskaya O.N., et al. Multipotent mesenchymal stem cells in renal transplantation. Transplantologiya. The Russian Journal of Transplantation. 2019;11(1):21–36. (In Russian). DOI:10.23873/2074-0506-2019-11-1-21-36

Kidney transplantation is the most effective treatment for the end-stage chronic renal disease that has been observed to increase in the incidence consistently in recent years. Despite the achievements in immunosuppressive therapy in patients after renal transplantation, the graft survival length has remained unchangeable during the recent few decades. Bone marrow-derived multipotent mesenchymal (stromal) stem cells (BM MMSCs) are known as a potential tool to influence this situation. Since their discovery in the middle of the XX century, their wide therapeutic potential in the transplantation of solid organs was demonstrated both in experimental and clinical trials. They have the ability to modify recipient's immune response and improve postoperative course, however, having a low level of

their own immunogenicity. MMSCs realize their properties through interactions both with the innate and adoptive immune system. Meanwhile, actual questions such as an optimal dosage and injection timing are still need answers. Actual experience of both experimental and clinical use of MMSCs in kidney transplantation has been analyzed in the present publication.

Keywords: bone marrow-derived multipotent mesenchymal stem cells, renal transplantation, tolerance, immunosuppression, recipient, rejection, immune response, inflammation, regeneration, immunogenicity

GCS, glucocorticosteroids
IST, immunosuppressive therapy
BM MMSC, bone marrow-derived multipotent mesenchymal stromal cell
GVHD, graft versus host disease
GFR, glomerular filtration rate
FOXP3, the protein whose expression is characteristic of T regulatory cells
MHC, Major Histocompatibility Complex
NK, natural killers

The number of patients suffering from chronic kidney disease has been growing steadily over the past decades; the key factors that has worsened the epidemiological situation include, alongside with traditional kidney diseases, an increasing prevalence of diabetes, hypertension, hypercholesterolemia, and an increase in life expectancy [1]. It is generally accepted that kidney transplantation is the most effective treatment for end-stage chronic renal disease. About 80,000 kidney transplantations are

performed worldwide annually. However, this number of surgical interventions is far from fully satisfying the need of the healthcare system for this procedure, since due to the pressing shortage of donor organs in the world, only 25% of patients on waiting lists, become recipients of renal transplants [2].

Despite all the advances in immunosuppressive therapy (IST), the functional lifespan of the transplanted organs and recipient survivals have not significantly increased over the two recent decades [3]. This is believed due to the long-term use of immunosuppressive drugs, their toxic effect on the graft, and the development of life-threatening complications [4]. In an effort to create conditions for a crisis-free postoperative course, to develop immunological tolerance, to reduce the need for using immunosuppressive drugs and the incidence of infectious complications, and also to improve the quality of recipient lives in the early and late postoperative period, the researchers focused their attention on multipotent mesenchymal stromal cells (MMSC), the use of which, according to the literature, has a positive effect on the postoperative course in organ transplantation [5].

The bone marrow multipotent mesenchymal stromal cells (BM MMSCs) became known to scientists in the 60s of the XX century, when their properties were first described, including their ability to be reproduced in vitro [6]. Nevertheless, for a major part of the last century, the main attention was focused on the bone marrow hematopoietic stem cells, which led to important discoveries in the physiology of that cell population, and also prepared the ground for their successful transplantation for the treatment of hemoblastoses, such as recurrent non-Hodgkin's lymphoma and multiple myeloma, etc. [7, 8].

A distinctive feature of MMSCs was their ability to differentiate into the mesodermal tissue cells, such as adipocytes, chondrocytes, osteocytes, and fibroblasts [9, 10]. The immunosuppressive effect of MMSCs cultured in vitro was first clinically demonstrated in 2004 in a patient suffering from acute lymphoblastic leukemia due to the development of graft versus host disease (GVHD) after hematopoietic stem cell transplantation [11]. From that time on, it was the bone marrow that became to be considered as the main source for obtaining MMSCs for clinical use. However, there are data demonstrating the ability to extract these cells from other sources, such as adipose tissue, amniotic fluid, placenta, tooth tissue, umbilical cord, etc., which proves the high prevalence of MMSCs in body tissues [5].

While studying the MMSC properties, they were found to have no specific markers, and, therefore, the International Society for Cellular Therapy defined the minimum list of criteria for their identification: MMSCs must carry on their surface the receptors for monoclonal antibodies CD73, CD90 and CD105, and not express CD34, CD14 and CD45. The same criterion for identifying MMSCs is their ability to differentiate into osteogenic, chondrogenic, and adipogenic directions, as well as their ability to adhere to plastic in cultivation under standard conditions (plastic-adhesive properties) [9].

Over the recent decade, MMSCs have attracted the attention of transplantologists as a means to treat the patients undergoing solid organ transplantation, for two reasons: MMSCs have a modulating effect on innate and acquired immunity systems, and are also able to induce an enhancement of graft regeneration processes by secreting proangiogenic and antifibrotic factors [12]. Today, the world has gained the experience in using MMSCs,

which demonstrates the ability of these cells to inhibit the rejection process, and to prolong the graft survival, but yet to induce the development of undesirable reactions, under certain circumstances [12-14].

The purpose of this work is to review the world experience of using MMSCs in kidney transplantation in the experiment and in clinic and to identify the conditions for their most proper use and to minimize adverse effects on the graft and recipient's body.

1. Exploring the feasibility of using multipotent mesenchymal stromal cells in organ transplantation at preclinical stage

As described above, MMSCs are involved in many physiological processes, including the immune response modulation, and damaged tissue repairs. Numerous mechanisms of their effect on the immune response have been identified and described so far, the MMSC immunomodulating potential among them being the most studied and important for transplantation.

1.1 Immunogenicity and immunomodulating properties of multipotent mesenchymal stromal cells in their interactions with innate and adaptive immunity systems

The MMSC ability to escape from being a target for recipient's immune response is one of the key features, which determines the interest to this cell population as a potential agent influencing the immune system. The reasons for the low immunogenicity of MMSCs remain incompletely understood. Their ability to "escape" the immune response is believed to be associated with: 1) a weak expression of the major histocompatibility

complex (MHC) class I molecules, which allows them to avoid recognition by natural killers (NK cells) and 2) the absence of MHC class II antigens and the costimulation molecules CD40, CD80, and CD86, which leads to T cell anergy [15].

Speaking about the MMSC effect on the innate immunity system, one should note that this effect applies to almost all of its components [17-24]. Thus, the presence of MMSCs in a sheep model of erythrocyte hemolysis showed that their production of H factor suppressed the complement system activation by inhibiting the conversion of C3 and C5 components of the complement into their active forms [16]. In addition, in the clinical trial of MMSCs in graft versus host disease (GVHD), it was shown that they bind small amounts of immunoglobulins and do not have the expression of MCP complement regulatory protein (CD46) and DAF (CD55), and are also protected from lysis by the complement system through the expression of the protector (CD59) [17]. The effect of MMSCs on neutrophils has been less studied. However, it is known that MMSCs, when co-cultivated with neutrophils and added to bacterial lipopolysaccharide medium, promote the recruitment of neutrophils into the focus of inflammation, provide the increased expression of their chemokine receptors, and enhance the response to bacterial agents due to an increased production of proinflammatory cytokines (IL- 8 and MIF) [18].

MMSCs have been found to inhibit IL-2 induced proliferation of resting NK cells in human cell culture, and also partially affect the proliferation of activated NK cells. It has also been revealed that MMSCs prevent the induction of effector functions, such as the cytotoxic activity and production of cytokines. This inhibitory effect is associated with an abrupt

decrease in the regulation of the expression on the surface of cells that activate the NK receptors NKp30, NKp44, and NKG2D. Meanwhile, the key mediators of MMSC-induced inhibition of NK cells are indoleamine 2,3-dioxygenase and prostaglandin E2 [19, 20]. At the same time, IL-2-activated NK cells also affect mesenchymal cells and are able to effectively lyse both allogeneic, and also autologous MMSCs [21].

Special attention in the scientific literature has been paid to the effect of MMSCs on dendritic cells. So, it is known that MMSCs are able to inhibit the monocyte differentiation into dendritic cells, but this effect is reversible [22]. In MMSC presence, the CD83 expression on dendritic cells is significantly reduced, indicating that the latter return to an immature state [19, 22]. It is also known that MMSCs block the ability of dendritic cells to return to the lymph nodes and present antigens to T-lymphocytes [23]. The effect of MMSCs also extends over macrophages. The interaction of these cells results in a shift in the balance between M1 and M2 macrophage populations towards the M2 phenotype that helps limiting the inflammatory immune response and stimulates reparative processes [24].

The impact that MMSCs have on the components of the acquired immunity system is neither less significant. One of the first experimental studies conducted by a group of Italian immunologists demonstrated that MMSCs significantly suppressed the proliferation of $CD4^+$ and $CD8^+$ T lymphocytes due to intercellular interactions and nonspecific mitogenic stimuli, without causing the apoptosis of effector cells. The authors showed in vitro that the phytohemagglutinin- or IL-2-activated T cell proliferation decreased significantly ($p=0.0005$) in a dose-dependent manner when MMSCs were added to the T-cell culture [25]. Later, in other studies that

investigated the MMSC properties, those findings were extrapolated on MMSC precursors, i.e. mononuclear cells. Researchers believe that the blocking of T-cell proliferative potential occurs due to blocking of the cell cycle in G0/G1 phases [26-28]. The MMSC ability to inhibit the proliferation and differentiation of immune system cells (Th1, Th2, and cytotoxic T lymphocytes) is realized mainly due to the production of immunologically active molecules such as indoleamine 2,3-dioxygenase, prostaglandin E2, and transforming growth factor β [29]. Moreover, MMSCs have been shown to be capable to inhibit the activity of various subpopulations of T-helper lymphocytes (not only Th1, but also Th17) [30]. An additional mechanism for reducing the immune response when using allogeneic MMSCs is the induction of T-regulatory cell formation by them [31].

The effect of MMSCs on B cells remains less studied. It is known that the MMSC presence in culture inhibits the differentiation of B lymphocytes, but it is not clear whether this is the result of their direct or mediated effect on B cells [32]. The recently obtained results indicate the ability of MMSCs to stimulate the regulatory activity of B cells [33]. MMSCs directly inhibit the differentiation of lymphoblasts into effector B cells. Moreover, with the co-cultivation of T cells with MMSCs, the latter indirectly contribute to an increase in the population of the IL-10 producing regulatory B cells , which have anti-inflammatory activity [34].

The MMSC reparative potential has also been demonstrated in a number of preclinical studies conducted by researchers from different centers. It is known [35] that MMSCs in damaged tissues are capable of participating in their recovery. Initially, there was an opinion that the main

contribution to the restoration of damaged tissues by MMSCs was due to their own transdifferentiation and replacement of dead cells [36]. More recent works have shown that MMSCs realize their regenerative potential by producing cytokines, antioxidants, and growth factors, which, in turn, pose their effect on the recovery processes by limiting the inflammatory and stress response, stimulating neoangiogenesis [37, 38]. In addition, there has been noted an anti-apoptotic effect of MMSCs on the fibroblasts exposed to adverse conditions, such as hypoxia, ultraviolet radiation, etc. [37]. A key role, as shown by a number of experimental studies, in the process of MMSC-contributed regeneration of damaged tissues is played by the vascular endothelial growth factor, which production is controlled by IL-8 and is regulated by the intracellular signaling pathway PI3k-Akt (the signaling pathway characteristic of most cells of phosphoinositide-3-kinase (PI3K) and AKT kinase enzymes [39, 40].

1.2 The effect of multipotent mesenchymal stromal cells on immunological tolerance

To date, a number of studies have been performed on experimental models to investigate the MMSC effects in solid organ transplantation. In most studies, the attention was focused on the ability of a given cell population to prolong the graft function and reduce a rejection intensity. In a number of studies, the authors attempted to identify the substrate by which MMSCs realize their potential in recipient's body. Those studies showed that MMSCs were capable to attenuate the transplanted organ rejection both by reducing the ratio of pro-inflammatory Th cells in the graft tissues and by increasing the population of T-regulatory cells. The described works were

carried out on the models of allogeneic rejection of the transplanted heart, skin flap, or kidney [14, 41–43]. In 2010, an Italian group of scientists in their study on modeling kidney transplantation in rats demonstrated the possibility of improving the kidney graft function (creatinine and urea levels) and reducing damage to the tubular system [44].

One of the key tasks in the completed experiments was to determine the optimal time of MMSC administration to the recipient for modulating the immune response and identifying the relationship with the occurrence of anti-/pro-inflammatory effects in the recipient. It was demonstrated that pre-transplantation infusion of cells autologous to the recipient was accompanied by a significantly increased functional survival of the transplanted kidney. ($p<0.05$) [45]. The cells infused before organ transplantation predominantly localized in the lymphoid organs and contributed to a significant increase ($p <0.05$) in the T-regulatory cell population compared to the control group. In contrast, MMSCs infused after transplantation localized mainly in the kidney graft where they stimulated the migration of neutrophils and the accumulation of C3 complement with the subsequent development of organ dysfunction. Those facts have in many ways confirmed that MMSCs can change the ratio between regulatory and effector cells ($CD4^+$ and $CD8^+$ lymphocytes) towards the former ones. In addition, Ge et al. showed that T-regulatory cells ($CD4^+$ $CD25^+$ FOXP3) were an essential element in the immunological tolerance induction in kidney transplantation, with the T-regulatory cell population being increased under the effect of indoleamine 2,3-dioxygenase produced by MMSCs [46]. Moreover, N.A.Onishchenko et al. in one of their studies demonstrated that a single infusion of autologous bone marrow MMSCs at a concentration of 0.3–0.5 x 10^6 cells per kg of

recipient body weight can exert a protective desensitizing effect on the transplanted kidney tissue being in a decentralization condition, and prolong the period of graft normal functioning without signs of severe destruction. Meantime, under the same conditions, high doses of MMSCs (3.0–5.0 × 106 cells per kg of body weight), on the contrary, led to started at 3 months of follow-up, and further increasingly progressed clinical symptoms (proteinuria, decreased diuresis) and histological signs (focal cell infiltration, protein masses accumulated in glomerular and tubular lumen) of chronic transplant nephropathy [47].

The above given preclinical data on the positive effects of MMSCs inspire hope for a possible extrapolation of the experimentally obtained results to humans with transplanted organs after controlled clinical trials have been conducted. However, the inclusion of MMSCs in the standards of medical care for recipients may be impeded by a number of factors that could not be taken into account in experimental work; among them, there is a significant change in recipient's immune status by the IST effect and the difference in inflammatory responses between animals and humans [48].

2. The experience of using multipotent mesenchymal stromal cells in clinical practice

The clinical use of the immunomodulating and regenerative effects of MMSCs in the treatment of various diseases remains promising today. A number of papers have been published on the successful use of MMSCs in chronic inflammatory diseases such as Crohn's disease, ulcerative colitis [49], and diabetes mellitus [50], as well as the GVHD occurring after bone marrow allotransplantation [51]. Moreover, drug regulatory authorities in

Europe and North America have already approved the use of MMSC-based drugs for the treatment of a number of diseases (GVHD, ulcerative colitis) [52, 53].

2.1. The beneficial effect of multipotent mesenchymal stromal cells on the graft function

To date, several studies on the use of autologous BM MMSCs in patients undergoing renal allotransplantation have been completed [54, 55] or are being under way [56]. The main objectives of these studies have been to achieve a recipient tolerance to a transplanted organ, improve the graft survival, minimize the immunosuppressive therapy [55].

A pilot clinical study on the safety and feasibility of therapy with the recipient autologous MMSCs in kidney transplantation was the work done by Perico et al [54]. On day 7 after surgery, two patients received an intravenous infusion of MMSCs at a dose of 1.7 × 106 cells/kg and 2.0 × 106 cells/kg of body weight for the 1st patient and for the 2nd patient, respectively. Additionally, basiliximab (20 mg intravenously before and on day 4 posttransplant) was used as an induction IST. In both patients, the laboratory study results in peripheral blood showed an increased population of regulatory T cells ($CD4^+$ $CD25^{++}$ $FOXP3^+$ $CD127^-$) to the values observed before the surgery, while the numbers of pro-inflammatory T cells ($CD8^+$ $CD45RO^+$) were reduced. Despite the presence of the above mentioned laboratory signs of an increasing tolerogenic status, transient acute renal failure was observed in both patients from day 7 to day 14. Later on, the authors, returning to making the experiments on mice, showed that, probably, attracting MMSCs in a transplanted kidney and increasing the renal damage

with the development of its dysfunction was caused by the fact that the cells entered the body in conditions of an inflammatory reaction, which resulted from ischemic and reperfusion injury to the graft in the early postoperative period [45]. Thus, the authors suggested that it would be advisable to administer MMSCs immediately prior to the donor kidney reperfusion. The efficacy of that approach was confirmed by Perico et al. at the second stage of the study [57]. Two patients who received low doses of rabbit antithymocyte globulin as an induction IST (0.5 mg/kg for 6 days, starting from the preoperative day), had the MMSC infusion performed a day before the kidney transplantation. None of those patients had a graft dysfunction in the postoperative period. The immune status monitoring demonstrated that those patients also had an increased number of T regulatory cells and a decreased number in pro-inflammatory T cells in peripheral blood.

Five years after completing the second stage of the study, the authors reported the results of a long-term follow-up (5–7 years) of patients in the treatment groups [58]. Additional patients were selected for the inclusion in the control group (n=12). The patients of the control group received basiliximab (20 mg intravenously before and on day 4 after surgery) as an induction IST or rabbit antithymocyte globulin (0.5 mg/kg for 6 days, starting from the pre-operative day). Cyclosporin A and mycophenolate mofetil were used in low doses as the baseline IST in all patients. Every 6 months, recipients were evaluated for their clinical and immunological status. All the followed-up subjects showed a stable function of the graft throughout the entire follow-up period. Compared with the control group, the MSC-treated patients showed significantly slower reduction in glomerular filtration rate (GFR) ($p < 0.05$). In 3 of 4 MSC-treated patients, there was a

significantly lower number of memory $CD8^+$ T cells compared with baseline values ($p<0.05$). In addition to the marked positive effects of MMSCs on the graft function and the development of immunological tolerance, an important result of the observation was the demonstration of the long-term comparability of the safety profiles between the MSC-treated patients and controls.

In many ways similar results were obtained in a pilot study conducted by a group of scientists in India in 2015 [59]. It was shown that intravenous administration of autologous MMSCs to the patients after kidney transplantation had a positive effect on the development of host tolerance to the graft. In that study, MMSCs ($0.2–0.3 \times 10^6$ cells/kg for the first 2 patients and $2.1–2.8 \times 10^6$ cells/kg for the 3rd and 4th patients) were administered to recipients a day before and at 30 days after surgery. As a maintenance IST therapy, the patients received tacrolimus (until a blood level of 4–8 ng/mL was reached), mycophenolate mofetil (1 mg, 1 time per day), and glucocorticosteroids (GCS) (up to 5 mg per day). Rabbit antithymocyte globulin (1 mg/kg for 3 days, starting from the preoperative day) was administered as an additional induction therapy. All patients from the main group showed satisfactory graft function and the absence of histological abnormalities in biopsy specimens taken at 1 and 3 months after surgery. Compared with the control group, the patients who additionally received MMSC therapy had a significantly higher number of T-regulatory cells ($p=0.04$). Another interesting researcher observation was also the increase in the number of CD4 T cells in patients of the main group, but the increase in that cell population was not accompanied by the increase in their proliferative potential and was not proportional to the increase in the number

of regulatory cells; all those confirmed clinically the effect of immune modulation and the development of transplantation tolerance.

In one of the largest, completed to date studies, which included 159 patients who underwent living-related kidney transplantation, an attempt was made to reduce the IST amount by MMSC infusion [60]. Three groups of patients were formed; the recipients of Group I (n = 53) received autologous MMSCs (1–2 × 10^6 cells/kg) before transplantation and on day 14 after surgery along with a standard therapy with calcineurin inhibitors (tacrolimus 0.12 mg/kg). In Group II, the patients (n = 52) received MMSCs in the same regimen, but in combination with a 20%-reduced dose of calcineurin inhibitor. The results used as controls were those of the patients (n = 51) who received induction therapy with anti-IL-2 receptor antibodies (20 mg at 2 hours after surgery and on day 4) and calcineurin inhibitors in standard doses (tacrolimus 0.12 mg/kg) without the additional administration of BM MMSCs. In all groups, immunosuppression also included the therapy with corticosteroids and mycophenolate mofetil as a maintenance therapy. Despite the fact that the patient and graft survival rates did not differ within 2 years, it was revealed that the incidence of the biopsy-confirmed graft rejection in Groups I and II was significantly lower ($p<0.05$) than in the control group. Besides, the graft function recovered significantly faster ($p<0.05$) with the administration of autologous MMSCs. In the first year after surgery, the recipients in the MSC groups showed a significant ($p = 0.05$) decrease in the incidence of opportunistic infections compared to the patients who received standard immunosuppression. The reduced infectious complication rate could be explained, besides using MMSCs, by the fact that the majority of patients in this study had a negative serological status

regarding cytomegalovirus infection. Unfortunately, the study protocol did not provide for immunological monitoring, and therefore, it is difficult to judge how the described positive effects were realized.

Thus, the administration of autologous BM-derived MMSCs just before kidney transplantation can be recommended as the means to improve the graft function, induce tolerance, and reduce the dose of immunosuppressants, which can significantly improve the outcomes of patients with chronic renal disease.

Recently, the results of studies on the feasibility of using allogeneic (donor and recipient) MMSCs in patients after kidney transplantation have been published [61, 62]. A group of scientists from China in their randomized study used umbilical-cord-derived allo-MMSCs (2×10^6 cells/kg infused via the peripheral vein before transplantation and 5×10^6 cells via the renal artery during surgery) as an addition to induction IST [61]. Patients of the trial group (n=21) and the control group (n=21) received antithymocyte globulin (50 mg/day) and methylprednisolone (500 mg/day) as induction IST for 3 postoperative days. The baseline IST included mycophenolate mofetil (1–1.5 g/day), either tacrolimus (0.1–0.15 mg/kg/day) or cyclosporine (6–8 mg/kg/day) starting from day 2–4, and methylprednisolone, its dose being reduced by 5 mg/day every week starting from day 4 (from 30 mg/day to 10-15 mg/day). Patients of the trial and control groups showed comparable results evaluated for the study primary end points, such as the graft survival ($p = 0.97$) and the recipient survival ($p = 0.15$), the incidence of the delayed graft function ($p = 0.15$) and acute rejection ($p = 0.63$), as well as the GFR ($p = 0.88$). Although the study did not demonstrate the clinical superiority of adding the cell therapy to the

standard treatment regimen, due to a small sample size and the used MMSC administration regime (a single systemic infusion), it showed that umbilical-cord-derived MMSCs can be used as a feasible and safe induction therapy.

Later, another group of researchers attempted to study the safety and tolerability of using a single infusion of allogeneic BM MMSCs as an adjunct to the standard IST [62]. The cells were infused on day 3 (±2) after kidney transplantation (1.5–3 × 10^6 cells/kg). The IST scheme in patients of the MSC-treated group (n=10) and the control group (n=10) included tacrolimus, mycophenolate mofetil, and GCSs from day 0 to day 4 together with anti-IL-2-receptor antibodies (IST drug doses were not reported in the publication of study results). Assessing the effect of MMSCs on the graft function, the researchers noted that on postoperative day 7, the GFR was significantly higher in the MSC-treated group ($p<0.05$). It was also shown that the use of MMSCs was associated with a significant increase in the population of $CD4^+$ T-regulatory cells" ($p<0.05$) in the absence of statistically significant differences in the number of B-cell populations. In the MMSC-treated group, the incidences of opportunistic infections and episodes of acute rejection were comparable with those in the control group ($p > 0.05$). Summarizing the results of their work, the authors noted that despite the observed superiority in a number of clinical and laboratory parameters, as well as the comparable safety profile, the further implementation of this technology into clinical practice requires more extensive studies investigating various MMSC dosages and administration regimens. Similar studies are being performed at the present time by independent groups of scientists.

2.2 Dosing and routes of administering multipotent mesenchymal stromal cells

To date, in the completed published studies, the dose and the multiplicity of the MMSC administration have been determined empirically. However, an understanding of the optimal dose and the MMSC dosing scheme are crucial for a large-scale implementation of this therapy into clinical practice. In the studies on MMSC administration in kidney transplantation, doses of 0.5×10^6 - 5×10^6 cells per kg of the recipient body weight were used [54–62], meanwhile, for treating other pathological syndromes and diseases, including GVHD, higher doses (up to 9×10^6 cells per kg of body weight) were allowed [63, 64]. An intravenous route of cell administration has proven to be quite effective and safe for a patient, including that in kidney transplantation. Additionally, the possibility of infusing cells directly into the graft or under its capsule was demonstrated, which contributed to a greater localization of cells in the graft and prevented their retention in the lungs [65].

2.3 Interaction of multipotent mesenchymal stromal cells with drugs for immunosuppressive therapy

An important issue that arises when discussing the clinical potential of this therapy is the drug interaction of MMSCs with immunosuppressive therapy. The lack of knowledge on this treatment method does not currently allow for research on patients with completely excluded IST. In this regard, it is important to understand the mechanisms by which the use of these means will affect the process of graft rejection. Completed studies can reveal the potential of these interactions. Buron et al. demonstrated an increased

immunomodulating effect of MMSCs in the presence of cyclosporin A, tacrolimus, an mTOR inhibitor in a mixed lymphocyte culture and no effect with the adding dexamethasone to the medium [66]. In addition to these data, another group of scientists showed that the MMSC preincubation with calcineurin inhibitors increases their immunoregulatory potential with respect to the proliferative activity of peripheral blood mononuclear cells [67]. On the other hand, besides the positive effect of MMSC therapy on various subpopulations of T-lymphocytes, the increased activity of T-regulatory cells also has an effect on the final results of the therapy [68]. A number of studies investigating the interactions of IST with MMSCs on animals also demonstrated an increased graft survival with the combined use of MMSCs with mycophenolate mofetil or with mTOR inhibitors [69, 70].

2.4 Safety of using multipotent mesenchymal stromal cells

One of the first questions arising at the initial stages of implementing any therapies is the safety of their use. Regardless of the IST type used, all patients after kidney allotransplantation have an increased risk of opportunistic infections and malignant neoplasms [71, 72]. Additional risks arising from using MMSCs are the complications such as the toxicity and immunogenicity of the cells to be administered [73]. To date, not a single case of an immediate toxic effect of MMSCs or the occurrence of malignant neoplasms was observed in clinical studies. However, a follow-up period in many completed studies was not long enough to make a detailed assessment of the incidence of complications in the long-term. Speaking on the incidence of opportunistic infections, one should note that currently there are

conflicting data about the MMSC effect on the risk of their occurrence [55, 59]. So, Tan et al. in their study showed a significantly reduced incidence of infectious complications. Other authors have reported a possible increase in the number of such complications associated with the administration of autologous MMSCs. Long-term follow-up (for 5–7 years) of a group of 4 patients after kidney transplantation, in whom MMSCs were used as an additional immunosuppression modality, showed no increase in the number of infectious complications or malignant neoplasms as compared to controls [58]. The experience of using MMSCs for other pathologies, such as GVHD, after allotransplantation of bone marrow hematopoietic stem cells indicates a tendency for an increase in the number of infectious complications [74, 75]. All these observations emphasize the need for a careful monitoring of adverse effects and require the development of appropriate protocols for the safe treatment of patients after the MMSC administration.

Conclusion

The presented data have clearly demonstrated a rapidly passed evolutionary path of implementing the use of multipotent mesenchymal stromal cells in patients undergoing kidney transplantation. The achieved results allow speaking about high therapeutic potential of MMSCs. The commenced clinical trials investigating this type of therapy must inevitably lead to large multicenter studies with defined endpoints, such as the graft survival, patient mortality, the incidence of acute rejection. The length of a follow-up period for these results to be monitored will also be important, as far as the currently available drugs for immunosuppressive therapy have already accumulated a long positive experience of use.

In the nearest prospect, from the point of practical implementation, it will be important to identify the effect of various dosage regimens and timing of administration on the process of the transplanted organ rejection, as well as to give a long-term efficacy assessment of adding the multipotent mesenchymal stromal cells in the complex of therapy for the recipient quality of life. These are the aspects that cause the greatest number of questions in regard to using this cell therapy method.

Conflict of interests. Authors declare no conflict of interests.
Financing. The study was performed without external funding.

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Information about authors

Natal’ya V. Borovkova, Dr. Med. Sci., Head of the Scientific Department of Biotechnologies and Tranfusiology at N.V.Sklifosovsky Research Institute for Emergency Medicine, ORCID: 0000-0002- 8897-7523;

Mogeli Sh. Khubutiya, Dr. Med. Sci., Prof., Acad. of RAS, President of N.V.Sklifosovsky Research Institute for Emergency Medicine, ORCID: 0000-0002-0746-1884;

Ol'ga N. Rzhevskaya, Dr. Med. Sci., Leading Researcher of the Kidney and Pancreas Transplantation Department, N.V.Sklifosovsky Research Institute for Emergency Medicine, ORCID: 0000-0001-6849-1457;

Aleksey V. Pinchuk, Cand. Med. Sci., Head of the Scientific Kidney and Pancreas Transplantation Scientific Department, N.V.Sklifosovsky Research Institute for Emergency Medicine, ORCID: 0000-0001-9019-9567;

Dmitriy A. Vasil'chenkov, Postgraduate in the Department of Transplantation and Artificial Organs, A.I.Yevdokimov Moscow State University of Medicine and Dentistry, ORCID: 0000-0002-2809-3929.