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USE OF MESENCHYMAL STEM CELLS IN SOLID ORGAN TRANSPLANTATION: CHALLENGES AND PROSPECTS (SYSTEMATIC REVIEW)

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Organ transplantation continues to be the gold standard for saving the lives of patients with end-stage organ diseases. Its goal is to help recipients live longer and better lives. However, despite advancements, organ transplantation still faces serious challenges, such as organ shortage and the effects of chronic immunosuppression. In this regard, there is ongoing vigorous search for therapeutic strategies that can improve the efficacy of allogeneic organ transplantation. Mesenchymal stems cells (MSCs) can significantly enhance and accelerate regenerative processes in damaged organs, can angiogenesis angiogenesis and inhibit cell apoptosis, inflammation and fibrosis formation, and have immunomodulatory properties. Researchers and physicians are interested in MSCs because of a set of unique properties that could be useful in solid organ transplantation. This review critically analyzes and summarizes the actual clinical data related to the study of the therapeutic effects of MSCs in organ transplantation. Electronic databases Medline/PubMed (www/ncbi.nlm.nih.gov/pubmed) and eLIBRARY/Russian Science Citation Index (https://www.elibrary.ru) were searched for relevant literature. Inclusion criteria were clinical use of MSCs to improve the condition of kidney, liver, lung, heart and pancreas recipients, and to enhance graft quality. Exclusion criteria for articles included the use of MSCs for the treatment of non-transplant patients, as well as articles detailing the effects of MSCs products (exosomes, vesicles and conditioned media) and research studies conducted *in vitro* and *in vivo* (without patient participation), conference proceedings, reviews and preprints of articles. Thirty-one original articles in English and Russian languages were selected for literature review. The prospects of MSCs in transplantology are also covered in the paper.

Keywords: mesenchymal stem cells, kidney transplantation, liver transplantation, lung transplantation, ex vivo perfusion, regenerative medicine.

INTRODUCTION

Organ transplantation continues to be the gold standard treatment for end-stage organ diseases. It is aimed at prolonging and improving the quality of life of recipients. In 2022, the number of organ transplants in the Russian Federation increased by 10.0% compared to 2021 [1]. While organ transplantation has significantly advanced in medical technology, it still faces serious challenges, such as organ shortage and the potentially harmful side effects associated with long-term immunosuppressive medications needed to prevent organ rejection in the recipient's body [2–5]. In this regard, the search for therapeutic approaches that can improve the effectiveness of allogeneic organ transplantation is actively pursued.

Mesenchymal stem/stromal cells (MSCs) have garnered significant interest in research and clinical practice because of their unique properties. By their nature, MSCs can be directed to differentiate into various mesenchymal tissues like cartilage, fat, and bone [6]. MSCs are also known to have immunomodulatory properties that make their allogeneic transplantation possible [7]. In addition, MSCs are accessible and there are no ethical restrictions in their use [8]. However, many researchers attribute the therapeutic potential of MSCs to the production of numerous regulatory and growth-stimulating factors, exosomes, microvesicles, lipoproteins, microRNAs, and apoptotic cells into the surrounding environment, which significantly enhance and accelerate tissue repair in damaged organs, stimulate angiogenesis, and prevent cell apoptosis, inflammation, and fibrosis formation [9]. The use of MSCs for the treatment of a wide range of pathologies has been reported, including cardiovascular [10, 11], neurodegenerative [12, 13], autoimmune [14, 15], lung [16], liver [17], kidney [18], orthopedic diseases [19], and coronavirus infection COVID-19 [20].

These properties highlight the significant potential of MSCs in solid organ transplantation. Incorporating MSCs into machine perfusion systems can enhance do-

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nor organ viability and function by mitigating ischemia-reperfusion injury (IRI) and promoting post-transplant tissue recovery [21]. At the same time, MSCs may serve as an adjunct immunosuppressive (immune-tolerizing) therapy to reduce postoperative complications [22].

This systematic review critically evaluates and summarizes the current clinical evidence on the therapeutic effects of MSCs in organ transplantation. Data were sourced from electronic databases, including Medline/PubMed (www.ncbi.nlm.nih.gov/pubmed) and eLIBRARY/Russian Science Citation Index (https://www.elibrary.ru).

DATABASES REVIEWED AND SEARCH RESULTS

The literature search was conducted in electronic databases Medline/PubMed (www/ncbi.nlm.nih.gov/pubmed) and eLIBRARY/Russian Science Citation Index (https://www.elibrary.ru).

The following terms were used as search query in Medline/PubMed: mesenchym*[ti] AND transpl*[ti] AND organ*[ti] (search query 1); mesenchym*[ti] AND transpl*[ti] AND liver*[ti] (search query 2); mesenchym*[ti] AND transpl*[ti] AND hepat*[ti] (search query 3); mesenchym*[ti] AND transpl*[ti] AND kidn*[ti] (search query 4); mesenchym*[ti] AND transpl*[ti] AND renal*[ti] (search query 5); mesenchym*[ti] AND transpl*[ti] AND heart*[ti] (search query 6); mesenchym*[ti] AND transpl*[ti] AND cardio*[ti] (search query 7); mesenchym*[ti] AND transpl*[ti] AND pancr*[ti] (search query 8); mesenchym*[ti] AND transpl*[ti] AND lung*[ti] (search query 9). Date of last search: 29.07.2024.

The following terms were used as search query in eLIBRARY: mesenchym* transpl* organ* (search query 1); мезенхим* транспл* орган* (search query 2); mesenchym* transpl* liver* (search query 3); mesenchym* transpl* hepat* (search query 4); мезенхим* транспл* печен* (search query 5); mesenchym* transpl* kidn* (search query 6); mesenchym* transpl* renal* (search query 7); мезенхим* транспл* поч* (search query 8); mesenchym* transpl* heart* (search query 9); mesenchym* transpl* cardio* (search query 10); мезенхим* транспл* серд* (search query 11); mesenchym* transpl* pancr* (search query 12); мезенхим* транспл* поджелуд* (search query 13); mesenchym* transpl* lung* (search query 14); мезенхим* транспл* легк* (search query 15). Date of last search: July 30, 2024.

The inclusion criteria for this analysis encompassed clinical studies investigating the use of MSCs to improve outcomes in kidney, liver, lung, heart, and pancreas transplant recipients, as well as to enhance graft quality. Only full-text original articles published in English and Russian were considered. Exclusion criteria included studies where MSCs were used for conditions unrelated to organ transplantation, research focusing on MSC-derived products (such as exosomes, vesicles, or conditioned media), and *in vitro* or *in vivo* studies that did not involve human patients. In addition, conference proceedings, review articles, and preprints were excluded.

The flow chart of literature search process is shown in Fig. 1.

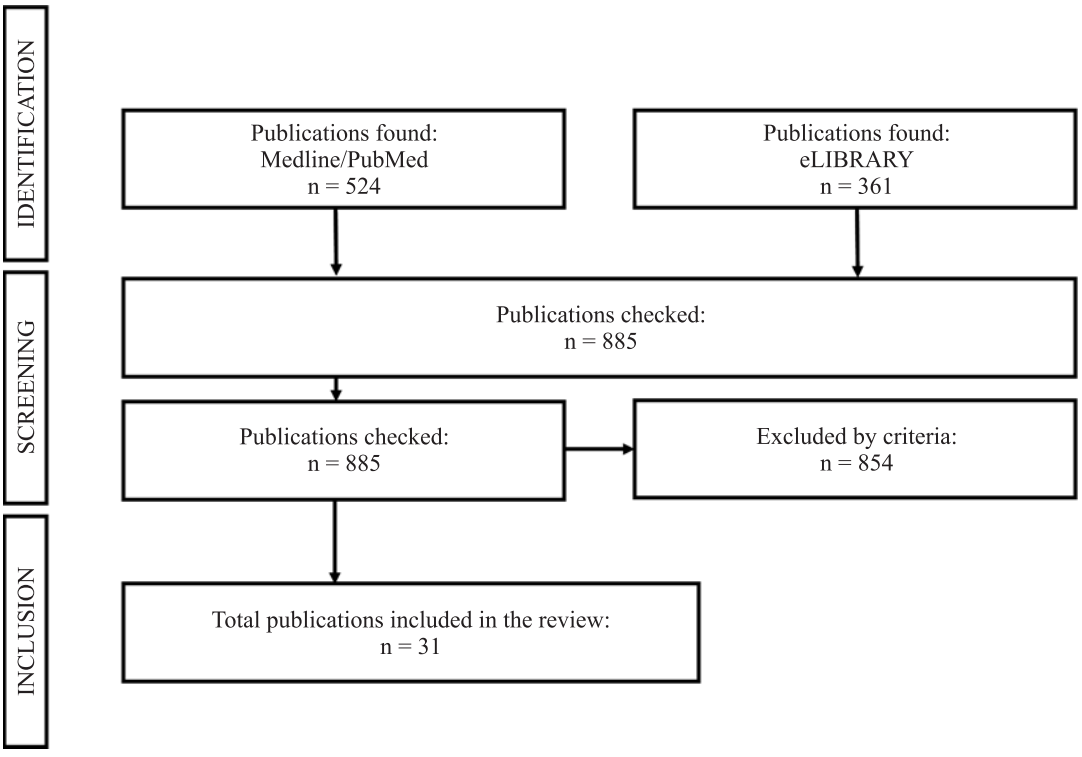

Fig. 1. Literature search flow diagram employed for this review

The initial search identified 885 publications. First, articles were manually excluded if they focused on MSC use in patients who had not undergone solid organ transplantation. Additionally, studies examining the effects of MSC-derived products, such as exosomes, vesicles, and conditioned media, were removed. Next, literature reviews and studies conducted under *in vitro* and *in vivo* conditions were excluded. In the final stage, 16 duplicate publications found in both PubMed and eLIBRARY databases were removed. As a result, 31 articles were included in the study [23–53]. Among the selected studies, 24 articles focused on patients who underwent kidney transplants [23–46], while 6 publications examined the effects of MSC administration in liver transplants [46–52]. One study explored the use of MSCs in lung transplantation [53]. No clinical studies reporting the use of MSCs in heart and pancreas transplants were found.

STUDY RESULTS

Findings from published studies indicate that both autologous and allogeneic MSCs are safe and exert a positive therapeutic effect in kidney, liver, and lung transplantation (Table). However, the extent of this effect varies among studies.

MSCs in kidney transplant

A key focus of many studies was evaluating whether immunosuppressive therapy could be safely reduced post-transplantation. For instance, Bezstarosti et al. reported that in the MSC-treated group, tacrolimus (Tac) dose was reduced by 50% during the second infusion of autologous MSCs and was completely discontinued after one week, whereas the control group continued Tac therapy. Two years post-transplant, renal function in the MSC group remained comparable to the control group, with no increase in rejection episodes [23].

Casiraghi et al. in a case report showed that infusion of autologous bone marrow-derived (BM-) MSCs in a living kidney transplant (KT) induces graft tolerance, which makes it possible to completely dispense with maintenance immunosuppressive drugs late after transplantation [28].

In a one-year follow-up of a phase I–II open-label trial involving 20 patients, Erpicum et al. demonstrated that a single infusion of allogeneic BM-MSCs after deceased-donor KT was safe, increased regulatory T cell (Treg) concentrations, and improved early allograft function. Notably, 30% of MSC-treated recipients did not require corticosteroids, compared to 40% in the control group [29]. However, long-term effects, including potential immunization against MSCs, remain to be investigated.

Dreyer et al. conducted a 12-month clinical study involving 10 kidney recipients from living (unrelated) donors. Their findings confirmed the safety of allogeneic BM-MSC infusion six months post-transplant in combination with low tacrolimus (Tac) concentrations (1.5–3.0 ng/mL). Following MSC administration, all recipients maintained stable kidney function, with no reported graft rejection or adverse effects related to cell therapy [44].

Peng et al. reported similar findings, demonstrating that allogeneic BM-MSC infusion enabled a reduction in Tac dosage from 0.077 ± 0.005 mg/kg/day to 0.045 ± 0.002 mg/kg/day in related donor kidney recipients. Importantly, this reduction was achieved without immediate or long-term toxic side effects associated with MSC administration. At 12 months of follow-up, only one acute rejection occurred in the control group, while all MSC-treated patients maintained stable kidney function with a 100% survival rate [38].

In a larger cohort, Pan et al. showed that a combination of reduced-dose Tac (0.04 ± 0.05 mg/kg/day) and allogeneic MSCs was as effective as the standard Tac regimen (0.07 ± 0.08 mg/kg/day) in maintaining graft survival for two years following living-related KT. No significant differences were observed in acute rejection rates, graft survival, serum creatinine levels, or glomerular filtration rate between the two groups [43]. These findings suggest that MSC administration may facilitate the use of lower doses of nephrotoxic calcineurin inhibitors (CNIs) post-KT.

Vanikar et al. reported a clinical case in which co-infusion of donor adipose-derived (AD-) MSCs and bone marrow-derived hematopoietic stem cells (HSCs) was administered before living-donor KT under nonmyeloablative conditioning. This approach successfully induced transplant tolerance, with stable kidney function maintained in the complete absence of immunosuppression for up to three years post-transplant [41].

Building on these findings, the authors conducted a prospective, open-blind randomized study involving 285 patients. Their results demonstrated the safety and efficacy of co-infusion of autologous AD-MSCs and bone marrow-derived HSCs into the portal circulation prior to KT. This strategy, combined with nonmyeloablative conditioning, effectively minimized the need for immunosuppression [42].

Meucci et al. demonstrated that autologous BM-MSC therapy, combined with complete Tac withdrawal, is a promising strategy for KT recipients. This approach not only effectively prevents graft rejection but also offers potential cardioprotective benefits [45]. A combination of MSC therapy with CNI withdrawal prevented progressive left atrial enlargement and dysfunction six months post-transplant [46].

In a study involving 53 patients, Wei et al. evaluated the efficacy and safety of allogeneic BM-MSC administration in kidney allograft recipients with chronic active antibody-mediated rejection. No adverse events such as fever, anaphylaxis, phlebitis, venous thrombosis, cardiovascular complications, or malignancies were observed following MSC therapy. The two-year allograft survival

rate was significantly higher in patients who received four doses of allogeneic BM-MSCs compared to the control group (87.0% *vs.* 66.7%) [26].

Reinders et al. demonstrated the feasibility, safety, and systemic immunosuppressive effects of two intravenous infusions of autologous BM-MSCs in kidney transplant recipients administered four weeks post-transplant. These recipients exhibited signs of rejection and/or increased interstitial fibrosis and tubular atrophy, highlighting the potential of MSCs in managing early post-transplant complications [39].

Similarly, Ban et al. confirmed the safety of four intravenous injections of allogeneic BM-MSCs, administered every two weeks, in two patients experiencing chronic active antibody-mediated rejection after kidney transplantation [27]. However, graft function deteriorated within six months after the final MSC dose, suggesting that MSC therapy may offer only short-term benefits in cases of prolonged antibody-mediated rejection resistant to conventional treatments.

Večerić-Haler et al. reported no positive effect of autologous MSC therapy in a patient with late antibody-mediated kidney rejection, occurring three years after transplantation. Within two months of follow-up, the patient experienced multiple complications, including nausea, vomiting, blepharitis, diarrhea, ascites, splenomegaly, arterial hypertension, proteinuria, and pancytopenia. All symptoms resolved following the removal of the damaged kidney [25]. The poor outcome was associated with parvovirus B19 infection introduced via the donor organ, underscoring the need to establish clear contraindications for MSC therapy in antibody-mediated kidney rejection.

Of particular interest is the clinical case reported by Dave et al. A patient with type I diabetes mellitus and end-stage renal disease received a combination therapy of allogeneic undifferentiated AD-MSCs, insulin-producing cells differentiated from AD-MSCs, and hematopoietic bone marrow cells one month before undergoing a living-donor KT. Remarkably, the patient maintained stable renal graft function for 13 months without signs of rejection or deterioration of diabetic status, despite continued administration of CNIs and steroids [40].

MSCs in liver transplant

Korotkov S.V. et al. reported a clinical case demonstrating the feasibility of minimizing Tac doses in cases of renal impairment associated with chronic liver transplant rejection. Their findings suggested that reducing Tac did not exacerbate immunological dysfunction and emphasized the necessity of multiple MSCs infusions to establish an adequate immunotolerant environment in the recipient [47]. Similarly, Detry et al. successfully reduced Tac doses in liver transplant recipients following allogeneic BM-MSCs infusion, without significant side effects or graft rejection, in contrast to the control group [51].

Mora et al. described a clinical case where MSCs were successfully used alongside cyclosporine and methylprednisolone to regulate the immune response in an liver transplant recipient experiencing graft-versus-host disease [49]. The authors emphasized the importance of considering individual patient factors such as disease severity, overall health status, and comorbidities. They also highlighted the necessity of continuous monitoring, including liver function assessment, infection rates, and potential complications, to enable timely adjustments in therapy.

Zhang et al. conducted a study with 82 patients diagnosed with ischemic cholangiopathy after deceased-donor liver transplant. The results showed that administering human umbilical cord-derived (UC-) MSCs to liver recipients was safe, with no significant MSC-related adverse events. UC-MSC therapy improved liver function, as indicated by decreased levels of total bilirubin, gamma-glutamyl transferase (γGT), and alkaline phosphatase at week 20 post-treatment. The need for interventional procedures (e.g., endoscopic retrograde cholangiopancreatography, stenting, percutaneous transhepatic cholangiostomy) was significantly lower in the MSC group (33.3%) compared to the control group (64.3%). Moreover, the 1- and 2-year graft survival rates were higher in the MSC-treated group than in the control group [52].

MSCs in lung transplant

Erasmus et al. found that the administration of allogeneic BM-MSCs may slow the decline in lung transplant function in recipients experiencing chronic rejection [53].

Our analysis revealed that most of the included studies (n = 23) utilized autologous or allogeneic BM-MSCs, while only five studies used AD-MSCs and one study used UC-MSCs; in two studies, the cell source was unspecified. Autologous MSCs were used in 11 studies, whereas allogeneic MSCs were used in 18 studies.

In one study, Kaundal et al. compared autologous and allogeneic BM-MSC infusion one day before and 30 days after KT from a related donor. The study found no dose-dependent toxicity from MSCs of different origins. Flow cytometric analysis showed an increase in B regulatory lymphocyte populations and nonconventional regulatory T cells (Tregs), along with a decrease in T effector lymphocyte proportions in patients receiving autologous MSCs. These preliminary findings suggest that autologous MSCs may be a safer option for reducing adverse immune responses, whereas allogeneic MSCs may trigger specific cellular and humoral immune responses against donor antigens [24].

The optimal number of MSCs required to achieve effective immunosuppression remains unknown, as do-

sage selection in studies is largely empirical and requires further investigation. The most commonly used MSC dose ranges from 1.0 to 2.0 × 10^6 cells per kg of body weight, while some studies have administered up to 5.0 × 10^6 cells per kg in a single infusion.

Of particular interest is the study by Mudrabettu et al., in which an initial lower dose of 0.21 × 10^6 cells per kg was administered to the first two patients before increasing to levels comparable to other studies. Regardless of the administered cell dose, recipients demonstrated an increase in Tregs populations and a decrease in T-cell proliferation [31].

Determining the optimal timing for MSC administration is crucial for the success of MSC therapy. In a pilot study involving two kidney recipients from a related donor, Perico et al. suggested that pre-transplant infusion of autologous BM-MSCs may be beneficial [36]. A subsequent study by the same authors demonstrated that a single pre-transplant infusion of MSCs did not negatively impact the kidney graft while maintaining therapeutic immunomodulatory effects. They also observed a correlation between Treg expansion and basiliximab induction therapy [32].

In a long-term follow-up study with a larger patient cohort, Perico et al. reported stable kidney graft function for 5–7 years after a single infusion of autologous BM-MSCs, alongside minimal maintenance immunosuppressive therapy. Importantly, their findings indicated that MSC infusion did not significantly increase susceptibility to infections or tumor development over the long term [30]. The main results of our study are summarized in Table.

Fig. 2 presents the overall screening results of scholarly publications on the use of MSCs in organ transplantation. The figure reflects the number of publications identified in the initial search, followed by the exclusion of studies focusing on conditioned media, vesicles, and exosomes, which were not within the scope of this review.

Fig. 2 highlights that the number of preclinical trials (*in vitro* and *in vivo*) significantly surpasses that of clinical trials by more than two times according to the Medline/PubMed search and over 1.5 times according to the eLIBRARY search. It should be noted that although no clinical cases of MSC use in heart transplantation have been reported, approximately 20 studies have explored this area. This suggests that MSCs in heart transplantation is an emerging field that is gradually progressing toward clinical application. Additionally, the presence of numerous literature reviews and commentaries in the search results underscores the growing interest and scientific focus on this evolving area of clinical research.

At first glance, the absence of publications on MSC use in pancreas transplantation may seem surprising. However, this can be explained by the successful application of co-transplantation of MSCs with pancreatic islets as an alternative approach to full pancreas transplantation [54–56].

Allogeneic islet transplantation is considered a viable treatment option for patients with type I diabetes mellitus who have had the disease for over five years, are aged 18 to 65 years, experience recurrent severe hypoglycemic episodes and/or glycemic instability, show lack of sensitivity to hypoglycemic states, and have undetectable C-peptide levels [57–61].

This alternative approach may explain the scarcity of clinical studies specifically investigating the use of MSCs in pancreas transplantation.

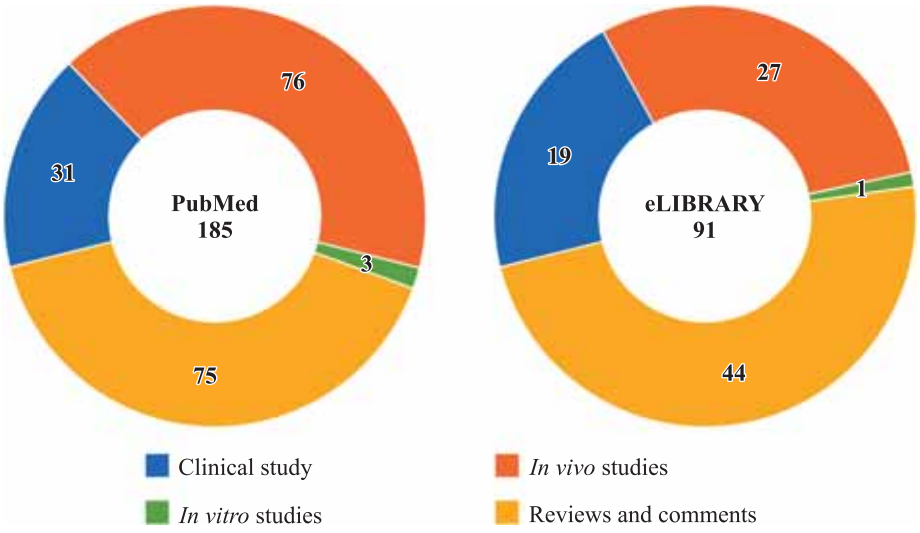

Fig. 2. Results of screening of scholarly publications covering the use of mesenchymal stems cells in organ transplantation in the electronic databases Medline/PubMed (www/ncbi.nlm.nih.gov/pubmed) and eLIBRARY/Russian Science Citation Index (https://www.elibrary.ru)

Table

General characteristics and results of studies included in this review

Publication	Patient group	Type of MSCs	Dose of MSCs	Administration route and frequency	Immunosuppressive therapy	Results
1	2	3	4	5	6	7
Kidney transplant						
Bezstarosti, 2023 [23]	70	Autologous (source not stated)	1.0–2.0 × 10^6 cells/kg body weight	IV at weeks 6 and 7 of transplantation	Tacrolimus, everolimus, prednisolone. In the MSCs group, tacrolimus dose was reduced to 50% during the second infusion of MSCs and completely withdrawn after 1 week, whereas in the control group, tacrolimus therapy was continued	MSC therapy promotes early tacrolimus withdrawal in living donor kidney transplant recipients: 45% of patients receiving MSCs were able to continue treatment without tacrolimus based on everolimus and prednisolone. The authors pointed out that more thorough research is necessary to establish precise criteria for prescribing MSCs as immunosuppressive therapy in KT
Kaundal, 2022 [24]	15	Autologous or allogeneic bone marrow-derived MSCs	1.0–1.5 × 10^6 cells/kg body weight	IV 1 day before transplantation and 30 days after transplantation	Tacrolimus, mycophenolate mofetil, prednisolone	Autologous MSC infusion was found to be safe and well tolerated by patients, and all recipients showed stable graft function following rejection episodes in a few cases. Differences in immunological responses were demonstrated regardless of the same origin, isolation, expansion conditions, and dosage of MSCs. The authors noted the need for more in-depth studies due to small sample size and lack of functional assessment data
Večerić-Haler, 2021 [25]	1	Autologous bone marrow-derived MSCs	3.0 × 10^6 cells/kg body weight	IV at 1-week intervals (1 week, 1 week, 2 weeks) 3 years after KT	Tacrolimus, mycophenolate mofetil, steroid	Lack of benefit after administration of autologous MSCs in a patient with late antibody-mediated kidney rejection. The patient was also diagnosed with parvovirus B19 acquired from donor organ
Wei, 2021 [26]	53	Allogeneic bone marrow-derived MSCs	1.0 × 10^6 cells/kg body weight	Regimen 1: 4 monthly IV Regimen 2: 4 weekly IV	Calcineurin inhibitors, mycophenolate mofetil with or without glucocorticoids, methylprednisolone	Immunosuppression combined with MSC infusion may slow down the decline in kidney allograft function in recipients with chronic active antibody-mediated rejection
Ban, 2021 [27]	2	Allogeneic bone marrow-derived MSCs	1.0 × 10^6 cells/kg body weight	4 IV every 2 weeks	Tacrolimus, mycophenolate mofetil, low-dose corticosteroid	Multiple doses of MSCs have been shown to be safe for treating chronic active antibody-mediated rejection in renal transplant recipients. Kidney function was stable during treatment with MSCs, then deteriorated within 6 months of the last MSCs infusion. The authors pointed out the need for more in-depth studies due to small sample size
Casiraghi, 2020 [28]	1	Autologous bone marrow-derived MSCs	2.0 × 10^6 cells/kg body weight	IV 1 day before transplantation	Cyclosporine, mycophenolate mofetil, methylprednisolone, prednisone	MSC infusion enabled a safe withdrawal of maintenance immunosuppressants while maintaining optimal long-term kidney allograft function

Continuation table

1	2	3	4	5	6	7
Erpicum, 2019 [29]	20	Allogeneic bone marrow-derived MSCs	2.0×10^6 cells/kg body weight	IV on 3 ± 2 days after transplantation	Cyclosporine, tacrolimus, mycophenolate mofetil, mycophenolic acid, azathioprine	One year after transplantation, 30% of MSC-treated patients did not require corticosteroids compared to 40% of the control group. It was shown that MSC infusion was safe and that early graft function improved. The authors noted the need for longer-term recipient follow-up
Perico, 2018 [30]	16	Autologous bone marrow-derived MSCs	2.0×10^6 cells/kg body weight	IV 1 day before transplantation or 7 days after	Cyclosporine, mycophenolate mofetil, prednisone	Pre-transplant infusion of MSCs in kidney transplant recipients from a related donor under low-dose maintenance immunosuppressive therapy is safe and does not cause serious side effects even with long-term follow-up
Mudrabettu, 2014 [31]	4	Autologous bone marrow-derived MSCs	First infusion: $0.35–2.1 \times 10^6$ cells/kg body weight. Second infusion: $0.21–2.26 \times 10^6$ cells/kg body weight	IV 1 day before transplantation or 30 days after	Tacrolimus, mycophenolate mofetil, prednisolone	MSCs were showed to be safe for patients who have had living-donor KT. MSC therapy expands regulatory T cells and reduces T cell proliferation. The authors emphasized the need for larger randomized studies to validate the findings
Perico, 2013 [32]	4	Autologous bone marrow-derived MSCs	2.0×10^6 cells/kg body weight	IV 1 day before transplantation	Cyclosporine, mycophenolate mofetil, prednisone	A single pre-transplant infusion of MSCs in recipients of a kidney from a related donor has no adverse effect on the graft, while providing a therapeutic immunomodulatory effect
Lee, 2013 [33]	7	Allogeneic bone marrow-derived MSCs	1.0×10^6 cells/kg body weight	Injection into the bone marrow of the right iliac bone	Calcineurin inhibitor, mycophenolate mofetil, steroids	The safety and feasibility of injecting MSCs into the iliac bone of living-donor kidney recipients was confirmed. No graft loss was detected. Three recipients experienced acute rejection
Tan, 2012 [34]	159	Autologous bone marrow-derived MSCs	$1.0–2.0 \times 10^6$ cells/kg body weight		Standard or 80% reduced dose of calcineurin inhibitors (tacrolimus, cyclosporine), mycophenolate mofetil, methylprednisolone	When compared to IL-2 receptor antibody induction therapy, the use of MSCs among related-donor kidney transplant recipients resulted in lower incidence of acute rejection, reduced risk of opportunistic infection, and improved kidney function at 1 year
Saadi, 2013 [35]	3	Allogeneic bone marrow-derived MSCs	$0.4–0.7 \times 10^6$ cells/kg body weight	2 IV with a 1-week interval	Cyclosporine, mycophenolate mofetil, prednisone	MSC therapy facilitates successful desensitization prior to a repeat KT
Perico, 2011 [36]	2	Autologous bone marrow-derived MSCs	1.7×10^6 or 2.0×10^6 cells/kg body weight	IV 7 days after transplantation	Cyclosporine, mycophenolate mofetil, prednisone	During MSC infusion, a kidney transplant from a related donor was found to be dysfunctional. The recipients were in good condition with stable graft function at 360 and 180 days after transplantation. The authors emphasized the need for more research on the undesirable side effects of MSC therapy
Vanikar, 2010 [37]	200	Allogeneic adipose-derived MSCs	–	Infusion into the omental vein 9 days before transplantation	Cyclosporine, prednisone, azathioprine	In the MSC + HSC group, 12% of recipients experienced acute rejection, 4% died, and there was no graft loss at 18 months after living-donor KT. In the HSC group, there was 18% of rejection episodes, 6% of graft loss and 9% of patients died

Continuation table

1	2	3	4	5	6	7
Peng, 2013 [38]	12	Allogeneic bone marrow-derived MSCs	First infusion: 5.0×10^6 cells/kg body weight. Second infusion: 2.0×10^6 cells/kg body weight	First infusion of MSCs directly into the renal graft artery during KT. Second infusion of MSCs IV after 1 month	Methylprednisolone, tacrolimus, mycophenolate mofetil, prednisolone	Tacrolimus dosage was lowered by 50% thanks to MSC therapy
Reinders, 2013 [39]	6	Autologous bone marrow-derived MSCs	$1.0–2.0 \times 10^6$ cells/kg body weight	Twice IV at 7-day intervals	Prednisone, tacrolimus or cyclosporine, mycophenolate mofetil	It is safe and clinically feasible to treat kidney recipients with subclinical rejection and/or interstitial fibrosis/tubule atrophy with MSCs
Dave, 2013 [40]	1	Allogeneic adipose-derived MSCs	1.1×10^4 cells/kg body weight	1 month prior to KT: infusion into the thymic bloodstream via femoral catheterization	Tacrolimus, mycophenolate sodium, prednisolone	Stable kidney graft function, no rejection, no worsening of diabetic status
Vanikar, 2013 [41]	1	Allogeneic adipose-derived MSCs	–	Portal infusion 16 days before KT	Methylprednisolone, prednisone	Achievement of graft tolerance with stable living-donor kidney graft function without immunosuppression at 6 months 3 years after transplantation
Vanikar, 2014 [42]	285	Allogeneic adipose-derived MSCs	4.6×10^4 cells/kg body weight	Infusion of cells into the omental vein 14 days before transplantation	Tacrolimus, prednisolone. The control group additionally received mycophenolate sodium	Patient survival at 7 years after living-donor KT under nonmyeloablative conditioning was 94.7% in the MSC + HSC group, 92.5% in the HSC group, and 78.4% in the control group. Graft survival rates for the same period were 94.6%, 86%, and 94.4%, respectively. The MSC + HSC group had the best outcomes, with the HSC group experiencing fewer rejection events and requiring less immunosuppression than the control group
Pan, 2016 [43]	32	Allogeneic bone marrow-derived MSCs	First infusion: 5×10^6 cells/kg body weight. Second infusion: 2×10^6 cells/kg body weight	First infusion of MSCs directly into the renal allograft artery during KT. Second infusion of MSCs intravenously 1 month later	Methylprednisolone, tacrolimus, mycophenolate mofetil, prednisolone	The combination of low-dose tacrolimus and MSC was as effective as standard-dose tacrolimus in maintaining graft survival for 2 years after transplantation
Dreyer, 2020 [44]	10	Allogeneic bone marrow-derived MSCs	$1.0–2.0 \times 10^6$ cells/kg body weight	Twice IV 6 months after transplantation	Tacrolimus, everolimus, prednisone	No acute rejection or graft loss was observed after administration of MSCs, renal function remained stable, and there were no marked changes in T- and B-cell populations or plasma cytokines. Administration of allogeneic MSCs combined with low-dose tacrolimus 6 months after transplantation is safe, at least for the first year after KT. The authors noted the need for further study of the efficacy of allogeneic MSCs in KT

Continuation table

1	2	3	4	5	6	7
Meucci, 2021 [45]	54	Autologous bone marrow-derived MSCs	1.0–2.0 × 10^6 cells/kg body weight	Twice weekly IV	Everolimus, prednisolone, tacrolimus	In KT recipients, MSC therapy combined with early tacrolimus withdrawal safely improves blood pressure control compared with standard-dose tacrolimus treatment 24 weeks after transplantation and attenuates adverse left ventricular remodeling characterized by myocardial hypertrophy and diastolic dysfunction. The authors pointed out the need for further studies to determine the impact of this promising immunosuppression regimen on long-term cardiovascular outcomes
Meucci, 2022 [46]	54	Autologous bone marrow-derived MSCs	1.0–2.0 × 10^6 cells/kg body weight	Twice weekly IV at weeks 6 and 7 post transplant	Everolimus, prednisolone, tacrolimus	A combination of MSC therapy and withdrawal of calcineurin inhibitors prevents progressive left atrial enlargement and dysfunction in the first 6 months after KT
Liver transplant						
Korotkov, 2022 [47]	1	Allogeneic adipose-derived MSCs	2.0 × 10^6 cells/kg body weight	MSCs infusion at days 392, 396, 400, 458 of transplantation	Tacrolimus, mycophenolate mofetil, medrol, certican	The efficacy of MSCs as an alternative way of immunosuppressive therapy was demonstrated, enabling to minimize tacrolimus doses in the development of renal damage against the background of chronic liver transplant rejection without running the risk of aggravating the severity of immunological dysfunction. The authors noted the need for further research on the use of MSCs in the late period after transplantation
Vandermeulen, 2021 [48]	10	Allogeneic bone marrow-derived MSCs	1.5–3.0 × 10^6 cells/kg body weight	IV at day 3 ± 2 of transplantation	Tacrolimus, mycophenolate mofetil	Infusion of MSCs did not cause infections or malignancies over 85 months of follow-up of liver recipients. No clear benefits for survival or graft function were found in the groups receiving and not receiving MSCs. The authors underlined the need for additional studies to better understand the effects of MSCs on transplanted organs
Mora, 2018 [49]	1	–	1.0 × 10^6 cells/kg body weight	MSCs infusion on day 35, 38, 42, and 47 of transplantation	Basiliximab, mycophenolate mofetil, tacrolimus, everolimus, methylprednisolone, cyclosporine	MSCs have demonstrated the potential to modulate the immune response in liver recipients against the background of graft-versus-host disease, which may lead to improved treatment outcomes and reduced the side effects of traditional immunosuppressive drugs. The authors recommended additional studies to better understand the mechanisms of action of MSCs
Casiraghi, 2020 [50]	20	Allogeneic bone marrow-derived MSCs	1.0–2.0 × 10^6 cells/kg body weight	IV during premedication	Tacrolimus, mycophenolate mofetil, methylprednisolone, prednisone	MSC infusion is safe, well-tolerated by liver recipients, does not cause infections or malignancies at 1-year follow-up, and promotes Tregs expansion. To validate the findings, the authors pointed out that a study with larger patient cohorts to confirm the results

End of table

1	2	3	4	5	6	7
Detry, 2017 [51]	20	Allogeneic bone marrow-derived MSCs	1.5–3.0 × 10^6 cells/kg body weight	IV on day 3 of LT ± 2 days	Tacrolimus, mycophenolate mofetil	No serious side effects and graft rejection were observed in liver recipients after MSC infusion in contrast to the control group. Additionally, MSCs made it possible to safely lower tacrolimus dosages
Zhang, 2016 [52]	82	Allogeneic human umbilical cord-derived MSCs	1.0 × 10^6 cells/kg body weight	IV at weeks 1, 2, 4, 8, 12, and 16 of diagnosis of ischemic cholangiopathy	Not specified	In liver recipients treated with MSCs, the need for interventional therapies reduced to 33.3% (64.3% in the control group) and graft survival increased at year 1 and 2 of follow-up
Lung transplant						
Erasmus, 2022 [53]	13	Allogeneic bone marrow-derived MSCs	0.5–1.0 × 10^6 cells/kg body weight	Single or repeated IV	Cyclosporine, mycophenolate mofetil, tacrolimus, prednisolone, azathioprine	Intravenous infusions of bone marrow-derived MSCs are well tolerated by lung transplant recipients with chronic rejection. In some patients, low doses of MSCs seem to halt the course of chronic obstructive pulmonary disease. The authors noted the need for more research to assess the efficacy of MSCs

Note: IV, intravenous infusion; MSCs, mesenchymal stem cells; KT, kidney transplant; LT, liver transplant; IL-2, interleukin-2; HSCs, hematopoietic stem cells.

Thus, the analyzed publications confirm the safety and therapeutic efficacy of MSC use in kidney, liver, and lung transplantation. MSCs exhibit regulatory potential, making them a promising tool for treating rejection reactions and inducing immune tolerance. They effectively suppress alloreactivity both before and after transplantation and may be suitable for prophylactic use during transplantation as well as for the treatment of rejection episodes post-transplant.

PROSPECTS FOR THE USE OF MESENCHYMAL STEM CELLS IN TRANSPLANTOLOGY

MSCs have shown promising potential in treating a variety of diseases including disorders of the nervous system and brain, liver cirrhosis, lung diseases, and cardiovascular diseases; they are also used in autoimmune diseases, for wound healing, in plastic surgery, etc., which has been confirmed by a large volume of preclinical and clinical trials [17, 19, 62–67]. The number of publications devoted to the use of MSCs for patient treatment is increasing. According to literature, 1426 clinical trials have been registered as of 2022, which is four times more than in 2013 [68]. The accumulated data revealed a number of potential mechanisms that explain the therapeutic effects of MSCs and the interest in them.

MSCs are multipotent cells capable of differentiating into multiple cell types, including osteoblasts (bone cells), chondrocytes (cartilage cells) and adipocytes (fat cells). In response to tissue injury signals and release of pro-inflammatory cytokines, MSCs secrete a variety of factors, including chemokines and cytokines, that promote regeneration and modulate immune responses. These include anti-apoptotic (STC-1, ECVs) and antifibrotic factors (bFGF, HGF), which help limit tissue damage and enhance healing, tissue precursor activators (TIMP-1, TIMP-2, TSP2, ECVs) and growth factors (TGF-β, VEGF, IGF1, HGF, KGF), which stimulate cell proliferation and differentiation, chemoattractants, which recruit endogenous precursors to the injury site, immune modulators (PGE2, TSG-6, ECVs), which locally regulate immune responses by selectively inhibiting immune cell proliferation (Fig. 3) [9, 69–71].

MSCs come from a variety of human tissue sources, such as bone marrow, adipose tissue, dermis, skeletal muscle, synovium, subcutaneous veins, dental pulp, umbilical cord-derived Wharton's jelly, amniotic fluid, lung and liver [8, 72]. Due to the diversity of MSCs sources, minimum criteria for identifying MSCs have been proposed by the International Society for Cell & Gene Therapy [6]: adhere to plastic when cultured under standard conditions; they must express the surface markers CD105, CD73 and CD90 and not express the surface markers CD45, CD34, CD14 or CD11b, CD79a or CD19 and HLA DR; MSCs must differentiate into osteoblasts, adipocytes and chondroblasts *in vitro*.

To use MSCs in clinical treatments, they need to be expanded in a lab to reach a large enough quantity, but this process of prolonged culturing can negatively impact

their important characteristics like phenotype, ability to differentiate into different cell types, and genetic stability, which is why careful monitoring is crucial to ensure their safety and effectiveness in therapy [73–75].

MSCs have been reported to have immunoregulatory properties, meaning they can suppress the proliferation, differentiation, maturation, and overall function of various immune cells [76–78]. MSCs have been shown to have the capability to activate regulatory T cells (Tregs) and regulatory B lymphocytes, which then function to suppress the activity of other immune cells, particularly effector and memory T cells [79]. In addition, MSCs have the capability to inhibit the development and maturation of dendritic cells (DCs), thereby significantly reducing their ability to activate T lymphocytes [80]. MSCs can induce tolerogenic DCs that produce interleukin-10 and promote Treg expansion [81]. MSCs have the ability to shift the phenotype of macrophages from a pro-inflammatory M1 state to an anti-inflammatory M2 state [82]. MSCs have also been shown to inhibit IL-2 mediated proliferation and cytotoxic activity of natural killer (NK) cells [83]. MSCs also produce significant quantities of chemokines, which attract immune cells to their location through a process called chemotaxis. Further, MSCs secrete immunosuppressive factors that act on migrating immune cells [84]. MSCs secrete a number of anti-inflammatory factors, namely, transforming growth factor (TGF-β), hepatocyte growth factor (HGF), nitric oxide, hemoxygenase-1, indoleamine-2,3-dioxygenase and express inhibitory costimulatory molecules such as, TRAIL and PD-L1 [85]. The activation of paracrine signaling pathways in the body by MSCs is of particular importance because isolated MSCs remain viable in the recipient body for a short period of time [86]. A recent study has revealed that when MSCs undergo programmed cell death (apoptosis) after being administered, this process is crucial in triggering immunosuppressive mechanisms within the body [87].

MSCs also have low immunogenicity, which allows the use of allogeneic cells. This feature of MSCs is associated with low expression of MHC class I molecules and absence of MHC class II, as well as costimulatory molecules B7-1, B7-2, CD80, CD40, CD40L and Fas ligand on the surface [88, 89].

Due to the above-mentioned properties of MSCs, their use arouses the interest of transplantologists as a means to develop a new therapeutic approach capable of improving the efficacy of treatment of solid organ recipients: MSCs possess immunomodulatory properties and can promote graft regeneration by releasing various bioactive molecules including exosomes, microvesicles, and soluble factors like growth factors, cytokines, and chemokines. There is strong evidence that MSCs have the potential to mitigate the severity of ischemic and reperfusion injury in multiple organs like heart, kidney, liver, brain, and lung [90–95].

Several key challenges complicate the clinical application of MSCs in organ transplantation. As shown

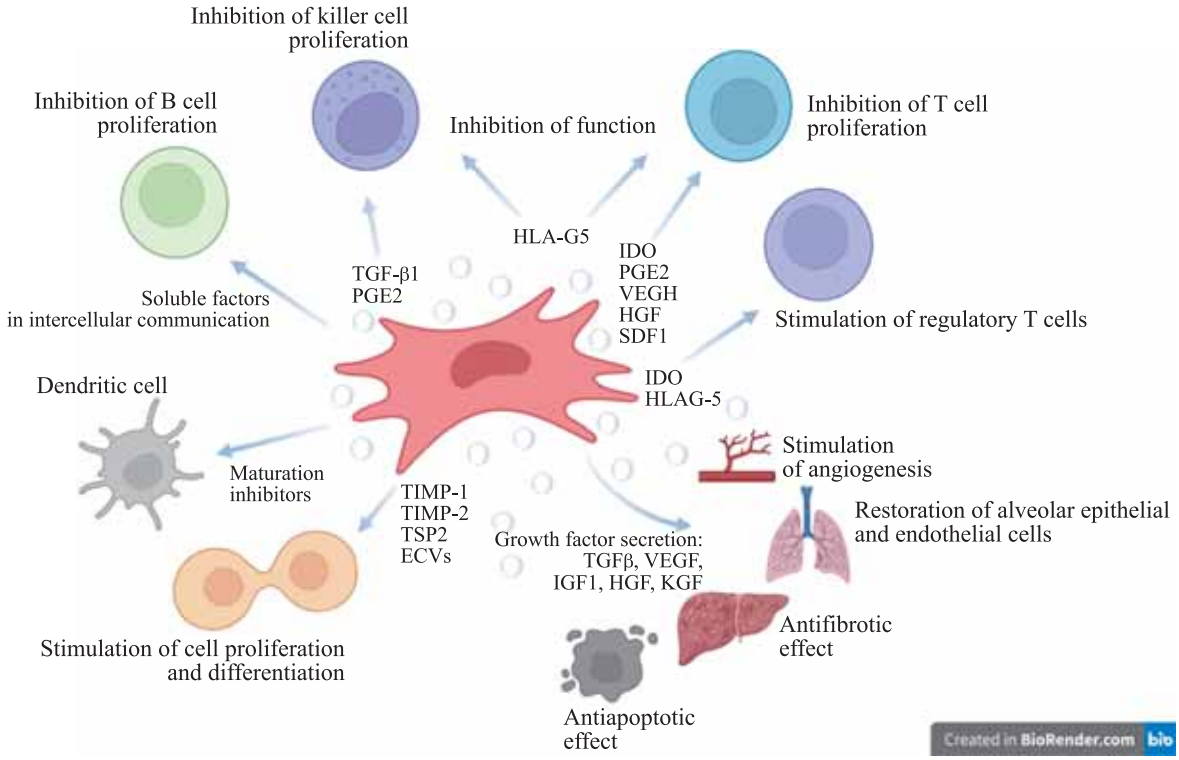

Fig. 3. Biological properties and effects of mesenchymal stem cells (MSCs). The figure was created using the BioRender.com program based on analysis of the collected database

in Table, MSCs from various sources have been used in clinical settings, yet studies indicate that their properties vary depending on their tissue of origin [96]. The heterogeneity of properties of MSCs from different donors remains an unresolved issue that may impact therapeutic outcomes [97].

The donor's age also influences MSC efficacy, as cells from older donors exhibit lower proliferative potential [98]. Furthermore, standardization of isolation and *in vitro* expansion protocols is crucial for maintaining MSC quality [99]. Current studies report significant variations in cell dose, infusion timing, and administration protocols, highlighting the need for standardized guidelines. Addressing these challenges is essential to optimizing the therapeutic efficacy of MSC therapy in transplantation.

Patients undergoing solid organ transplantation typically receive a combination of immunosuppressive drugs (ISDs) such as CNIs, corticosteroids, and mTOR inhibitors [100–102]. As discussed earlier, MSCs also exhibit immunosuppressive properties and may help mitigate the adverse effects of ISDs on the immune system [103].

Given these potential benefits, clinical trials have explored the use of MSCs as an adjunct to ISDs to enhance transplant outcomes. However, the interaction between MSCs and ISDs remains poorly understood, making it a crucial area for further research. For instance, Eggenhofer et al. demonstrated in a mouse model that different combinations of cyclosporine, everolimus, and mycophenolate mofetil with MSCs had varying effects on heart transplant survival [104].

Machine perfusion technologies have ushered in a new era in organ transplantation [105–108]. By preserving organs under near-physiological conditions, these technologies not only extend preservation time but also enable more accurate assessments of organ function [109]. Moreover, the ability to introduce drugs or cells into the perfusion solution presents an opportunity for targeted regeneration of ischemic organs.

This potential highlights the feasibility of integrating regenerative medicine approaches, particularly MSCs, into machine perfusion. MSCs offer therapeutic benefits through their ability to stimulate tissue metabolism, promote cell proliferation, and exert immunomodulatory, antiapoptotic, and antifibrotic effects. Several studies have demonstrated promising outcomes with MSC administration during machine perfusion of the kidney, liver, and lung [110–112].

As research in this field progresses, standardized protocols for MSC dosing and timing in *ex vivo* machine perfusion may be established, taking into account the organ type, size, and extent of ischemia-reperfusion injury [113].

Advancements in the use of MSC for transplantation are increasingly linked to their pre-activation strategies, one of which involves autophagy modulation [114]. Autophagy plays a crucial role in regulating MSC stemness, viability, differentiation potential, immunomodulatory properties, and pro-angiogenic activity. Enhancing MSC function through autophagy modulation before administration presents a promising approach to improving their therapeutic efficacy in organ transplantation.

By activating MSCs via autophagy modulation, their post-implantation survival can be extended, and the secretion of regulatory molecules – including growth factors, exosomes, microvesicles, lipoproteins, and miRNAs – can be enhanced. These factors accelerate tissue repair, promote angiogenesis, and mitigate apoptosis, inflammation, and fibrosis in transplanted organs [115–117].

Another method for MSC activation involves the use of scaffolds (carriers, matrices), which serve as biomimetic extracellular matrices. Scaffolds provide structural support that prolongs MSC viability and functional efficacy, ensuring an optimized microenvironment for them [118].

CONCLUSION

A review of publications in electronic databases suggests that MSC therapy holds promise for improving outcomes in kidney, liver, and lung transplantation, as well as enhancing graft quality. Studies have explored various MSC sources, dosing regimens, and immunosuppressive protocols. The scarcity of clinical trials further underscores the need for additional research to refine therapeutic protocols.

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