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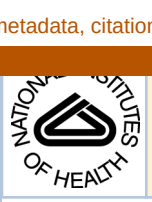

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Mesenchymal Stem Cells in Solid Organ Transplantation (MiSOT) 4th meeting: Lessons learned from first clinical trials

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Abstract

The 4th expert meeting of the MiSOT (Mesenchymal Stem Cells in Solid Organ Transplantation) Consortium took place in Barcelona on the 19th and 20th of October 2012. This meeting focused on the translation of pre-clinical data into early clinical settings. This position paper highlights the

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main topics explored on the safety and efficacy of mesenchymal stem cells (MSC) as a therapeutic agent in solid organ transplantation and emphasizes the issues (proper timing, concomitant immunossupression, source and immunogenicity of MSC and oncogenicity) that have been addressed and will be followed up by the MiSOT Consortium in future studies.

Keywords

Mesenchymal Stem Cells; Transplantation; Immunomodulation; Position paper

The MiSOT (Mesenchymal Stem Cells in Solid Organ Transplantation) Consortium was founded to enable effective collaboration between research groups working in the application of adherent stem cell products in solid organ transplantation (1–2).

The research teams involved in the innovative use of mesenchymal stem cells (MSC) in solid organ transplantation aim to bring tangible benefits to the clinical transplant setting, improving transplant outcomes and patient quality of life. The main goals of the MiSOT meeting are to foster the continued cooperation between members of the community and to discuss the challenges faced in advancing the application of MSC in clinical transplantation and how these should be addressed.

Clinical application

MSC are one of the most promising cell populations for cell-based immunomodulatory therapy in solid organ transplantation. During the last 2 years MSC have been applied to the clinical setting in several phase I trials (3–5) and developments in ongoing or trials nearing initiation (Detry et al-Liege (6), Remuzzi et al-Bergamo (7), Dahlke et al-Regensburg (8) communications at 4th MiSOT meeting and registered trials) were presented at this meeting. To date, MSC administration in clinical transplantation has proven relatively safe and feasible (Table 1). There are indications of efficacy in preventing acute cellular rejection and reducing induction and maintenance immunosuppressive regimens (4), inducing long-term stable graft function (3) and reducing tubulitis and interstitial fibrosis/tubular atrophy in some patients (5). In addition, MSC may induce systemic alloimmune modulation, since a donor specific down regulation of the proliferation of peripheral blood mononuclear cells was reported (5) and the ratio of regulatory T cells (Tregs) versus memory T cells was increased (3).

The outcomes of these trials have highlighted several issues (proper timing, concomitant immunosuppression, source and immunogenicity of MSC and oncogenicity) that need to be promptly addressed. This needs to be supported by applied research regarding specific primary end-points and reference controls. It is clear that new evidence from basic research can provide valuable information for the design of future clinical trials.

The timing of therapeutic MSC administration remains a matter of intense debate. Depending on the therapeutic goal and concurrent immunosuppressive drugs, different timing of MSC administration will be necessary. To induce a more tolerogenic state and prevent early acute rejections, MSC may be given around the moment of transplantation. However, while early post-transplantation injection promoted long-term pro-tolerogenic effects, it also induced transient renal dysfunction in two kidney transplant recipients (3). Therefore pre-transplantation infusion of MSC is now investigated. For treatment of ongoing (subclinical) chronic rejection, MSC may be given later after transplantation when graft function is still stable or when graft function is deteriorating. In the only clinical study so far administering MSC six months after transplantation, kidney function remained stable. The long term effects of MSC on chronic rejection are still awaited.

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The choice of concomitant immunosuppression is another point of discussion. Preclinical studies suggest that Mycophenolic acid/Mycophenolate mofetil (MPA/MMF) may have a synergistic immunomodulatory effect with MSC (9) while calcineurin inhibitors (CNI) may not do so (10). However, the safety trials published so far in kidney transplantation used CNIs as concomitant immunosuppression. This suggests that distinct drug combinations in association with MSC open an avenue of improvement for future clinical trials. Further, the use of induction therapy is still at an exploratory stage. Tan et al. (4) suggest that MSC can substitute the induction therapy with anti-IL-2 receptor (Basiliximab), whereas Perico et al. (3) concomitantly used Basiliximab and T cell depletion (Thymoglobulin) as induction therapy to facilitate the immunomodulatory properties of MSC.

The tissue source of MSC is an important area of consideration for future phase II/III trials. Besides BM-MSC, emerging data also suggest the high therapeutic potential of MSC isolated from adipose tissue (AT), cord blood (CB) and other human tissues. Some of these tissues are easily accessible and may therefore represent a suitable source of MSC.

In addition to the tissue source, the immunogenicity of MSC may have both economic and logistic implications and impact on the viability of MSC-based therapies. MSC are very likely not completely immunoprivileged as they express HLA class I and can be induced to express HLA class II. The use of autologous MSC has been the choice of treatment of kidney transplantation trials so far; in this regard, in renal transplantation autologous MSC from uremic patients might be used as MSC from end-stage renal disease patients have proven as efficiently immunosuppressive as those from healthy individuals (11)(12). However, some recently designed trials have focused on the use of allogeneic MSC produced in either in-house GMP facilities or by commercial cell production companies. The availability of an off-the-shelf product commercially produced may overcome some of the logistic limitations associated with autologous MSC in the organ transplant setting and allow institutions without GMP facilities or a capacity to isolate MSC to actively participate in this field of research. Moreover, the allogeneic MSC product can be easily standardized and therefore provides more comparable results among different trials. Standardized expansion is a critical point since specific effects of expansion details can induce variation in the product efficacy and is a concern of the group that is seeking for new ideas to overcome this inter-trials disparity. Although the immunogenicity of allogeneic MSC needs further study to prove safe in clinical trials, a very recent pilot study showed that donor-derived bone marrow MSC safely allowed reduction of conventional dose of tacrolimus in living-related kidney transplant recipients, at least during 12 months follow-up (13). So, results obtained from ongoing trials are eagerly awaited in order to give a better judgment regarding this problem and make a decision on how to proceed.

Encouragingly, the potential for MSC maldifferentiation, an area of concern for the transplantation community and the MiSOT group in particular, may be less of an issue than previously thought. Multiple studies have failed to find evidence for malignant transformation of MSC (14). Indeed earlier reports on the MSC maldifferentiation have been retracted following evidence that the MSC cultures reported were contaminated with tumor cell lines (15–16). However, as research into MSC malignant transformation is ongoing, investigators must remain cautious on the interpretation of such findings.

Another focus of safety concerns in current clinical applications with MSC is a potential increased susceptibility to opportunistic infections. Reinders et al (5) reported the development of opportunistic viral infections in 3 out of 6 patients, indicating that care should be taken with the potency of the immunosuppressive effect of MSC. In contrast Tan et al (4) showed a reduced susceptibility to infections in their MSC-treated patients compared to the regular immunosuppressive regimen. The effects of MSC

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immunosuppression need to be carefully analyzed and if necessary exclusion criteria defined before moving forward with MSC-based therapy in organ transplantation.

Regulatory aspects

The goal of reducing severe side effects of pharmaceutical immunosuppression justifies attempts to implement novel cellular therapies. While many authorities remain apprehensive of emerging cell-based immunomodulation therapies, one must be mindful that regulatory agencies face a struggle to ensure that regulations and guidelines keep pace with the development of new technologies. The differing regulatory requirements between the EU and the USA exacerbate this situation further.

In Europe, centralised and national regulations contain provisions for several cell therapy development strategies (17). Certain cell therapy applications may not follow the classical medicinal product development process with standard clinical trials. The European regulatory framework provides an option for cell therapy products under a Hospital Exemption (HE) clause. In order to qualify for HE, cell therapy products have to be prepared on a non-routine basis according to specific quality standards, and have to be used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner. Since HE is not a centralised procedure and Member States have to introduce national implementation tools, the requirements and conditions for the authorisation will vary from country to country. Activities required to implement the HE clause should be accomplished in the majority of the EU states by the end of 2012. Nevertheless, currently, it is uncertain if HE is the most promising approach of cellular therapy development for either the scientific, medical or commercial communities in Europe.

Centralised evaluation by the European Medicines Agency is required for cell therapy product marketing authorisation in the EU. Whilst there have been no MSC-based medicine authorisations in the EU, a number of MSC and other cell therapy products are marketed under conditional marketing authorisations in other regions (17).

The challenges of transferring a cell-based therapy from bench to bedside under a regulatory framework that crosses multiple responsible authorities, EU members and continents are difficult to overcome but in the meeting we learned that such translation is feasible.

Experimental news

Pre-clinical studies have revealed that although MSC remain in circulation for a very short period of time (18), a powerful therapeutic effect is observed. This opens the door to speculate about mechanisms of MSC action and may provide an indication to the importance of interactions between MSC and the innate immune system that might shape MSC responsiveness (reviewed in (19)). Preliminary results obtained from mice injected with syngeneic MSC show a transient induction of inflammatory mediators, while later being protected from the mounting of inflammatory reaction in response to LPS (Hoogduijn et al, Communication at the 4th MiSOT meeting).

This phenomenon leads to the gradual removal of MSC from the recipient and has regulatory implications. The host-controlled, transient presence of MSC may reduce the concerns regarding the persistence of implanted cells longer than required, while preserving their therapeutic efficiency.

The study of the immunomodulatory properties of MSC and the insight already gained on their mechanisms of action will contribute to develop more refined therapeutic approaches. Besides the well-known effect on T cell proliferation, new and improved studies have

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unraveled the effect of MSC on the induction of Tregs, Th17 cells and regulatory macrophages depending on the inflammatory milieu encountered as well as a direct effect on B cells inhibiting their differentiation into immunoglobulin producing plasmablasts.

MSC possess a broad therapeutic spectrum in transplantation, being efficient not only in alleviating the alloimmune reaction but also in reducing the cell infiltrates and inflammatory mediators involved in ischemia/reperfusion injury.

In addition, beyond the attractive intrinsic features of MSC, their potential use as vectors or biological factories (cytokines, chemokines, receptors, growth factors) through *ex vivo* genetic engineering might allow additional therapeutic benefits to enhance organ transplantation outcomes.

Conclusions

In 2012, the MiSOT Consortium shared the experiences gained from the first clinical trials performed using MSC in solid organ transplantation and new pre-clinical and experimental studies. The results are encouraging, but additional knowledge is required before MSC-based therapies can be broadly applied to patients. Well designed trials with clearly defined end-points, appropriate controls and extensive immune monitoring are the key to succeed with the advancement of MSC therapy. The MiSOT expert meeting learned how MSC therapy has already proven safe in clinical trials and effective in preclinical models and highlighted the work required to translate this into a mainstream therapeutic approach.

Abreviations

MSC	Mesenchymal Stem Cells
MiSOT	MSC in Solid Organ Transplantation
Tregs	Regulatory T cells
EU	European Union
USA	United States of America
HE	Hospital Exemption
LPS	Lipopolysaccharide

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Table 1

Current published and ongoing clinical trials applying MSC in solid organ transplantation.

Registration number	Trial name	Status	Registration Date	Sponsor	Reference	Main results
NCT00658073	Induction Therapy With Autologous Mesenchymal Stem Cells for Kidney Allografts	Completed	April 8, 2008	Fuzhou General Hospital	Tan et al (4)	Compared with anti-IL-2 receptor antibody induction therapy, the use of autologous MSCs in kidney transplant recipients resulted in lower incidence of acute rejection, decreased risk of opportunistic infection and better estimated renal function at 1 year.
NCT00752479	Mesenchymal Stem Cells Under Basiliximab/Low Dose RATG to Induce Renal Transplant Tolerance	Recruiting	July 23, 2008	Mario Negri Institute for Pharmacological Research	Perico et al (3)	Findings from this study in the two patients show that autologous MSC infusion in kidney transplant recipients is feasible, allows enlargement of Treg in the peripheral blood, and controls memory CD8 T cell function.
NCT00734396	Mesenchymal Stem Cells and Subclinical Rejection (Measure)	Completed	August 13, 2008	Leiden University Medical Center	Reinders et al (5)	In kidney transplant recipients with subclinical rejection and interstitial fibrosis and tubular atrophy (IF/TA) treatment with autologous bone marrow MSC is clinically feasible and safe, and the findings are suggestive of systemic immunosuppression.
-	-	-	-	SunYat-sen University and Guangzhou Medical University	Peng et al (13)	The use of donor-derived MSCs in kidney transplant patients is safe and could provide potential benefits by reducing the dosage of Tacrolimus that is required to maintain long-term graft survival and function.
Eudra CT 2009-017795-25	Safety and feasibility of multipotent adult progenitor cells for immunomodulation therapy after liver transplantation: A phase I study of the MiSOT study consortium	Recruiting	November 28, 2011	University Hospital Regensburg	Popp et al (8)	Not published yet
NCT01429038	Mesenchymal Stem Cells After Renal or Liver Transplantation	Recruiting	September 1, 2011	University Hospital of Liege	-	Not published yet

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