Parameters Influencing Safety and Efficacy of the Ovarian Cell Therapy

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Despite the fact that several infertile couples can be successfully treated, one category of infertile patients still remains highly challenging for clinicians. This category refers to patients diagnosed with ovarian insufficiency.

Premature ovarian failure (POF) is a heterogeneous clinical syndrome defined by loss of ovarian activity before the age of 40. POF affects 1–2% of women of reproductive age and is influenced by ethnicity.

manifests as amenorrhea and infertility[1–3]. The annual incidence of POI has been steadily increasing[4,5]. Approximately 70% of POI cases are idiopathic, and while evaluation is warranted to identify the underlying etiology[6], in many cases it is not clear. Iatrogenic POI

It should be noted that 5–10% of women with POI might have spontaneous follicular development, menses resumption, or spontaneous pregnancies, especially during the first year after diagnosis.

There are different types of stem cells that can be derived from numerous sources include bone marrow stem cells, placenta MSCs, endometrial MSCs, and adipose derived stromal cells (ADSCs).

Oocyte Donation

Artificial Gametes

Artificial Ovary

Ovarian Tissue Transplantation

Platelet-Rich Plasma Intra-Ovarian Infusion

Mitochondrial Replacement Therapy

Stem Cell Transplantation

Stem cell therapy seems to be a promising approach. Nonetheless, in order to safely recruit it in clinical application toward treating ovarian insufficiency in the context of infertility, it should be highlighted that it is equally imperative to consider both strengths and weaknesses.

Despite the fact that mesenchymal stem cells are characterized by a low immunologic profile, allogeneic stem cell transplantation could lead to severe graft rejection, posing a risk for the patients' health.

With the rise of regenerative medicine, different types of SCs have been tested for follicular rescue and regeneration of the ovarian niche.

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Parameters Influencing Safety and Efficacy of the Ovarian Cell Therapy

As the firsts reports of spontaneous pregnancies achieved after bone marrow transplantation in oncologic women with primary ovarian insufficiency, increasing evidence supports the regenerative effects of stem cell-based therapies in the ovarian niche. Adult stem cells from several origins promote follicular development, increase ovarian local vascularization, increase follicle and stromal cell proliferation and reduce cell apoptosis and follicular atresia, although they do not modify embryo quality. Therefore, residual quiescent follicles of aged or damaged ovaries might produce competent oocytes in an adequate ovarian environment. Nevertheless, further research is needed to properly evaluate underlying mechanisms, identify best cell sources and design less invasive infusion techniques.

Influencing Factors on Safety & efficacy

Etiology & Underlying Mechanisms

Patient Selection

Cell Source

Administration Techniques

Safety Issues

Complications

Etiology & Underlying Mechanisms

Physiological

Genetics

Autoimmune disorders,

Environmental factors (Pollution, Infectious),

Iatrogenic (Surgeries, Oncologic ,Gonadotoxic)

Idiopathic situations.

Age

Patient Selection

This fact underlines the need not only to develop different strategies to improve clinical management of these patients, but also the importance of the selection of the right population of POI patients, who can benefit from each approach.

Cell Source

Bone marrow

Placenta MSCs

Human Menstrual Blood-Derived Endometrial Cells

Adipose derived stromal cells (ADSCs).

Amniotic Epithelial Cell (AEC) and Amniotic Mesenchymal cells (AMSCs) Umbilical cord

Autologous Cell Ovarian Transplantation (ASCOT)

Bone Marrow

Stem cell source appears to be an important factor. Several spontaneous pregnancies indicate that BMDSCs can recover ovarian function in patients with POI because of cancer treatment.

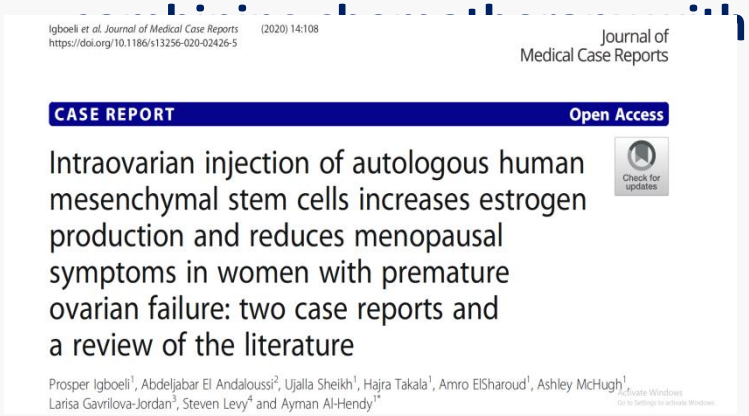
On the basis of this evidence, BMDSCs found to reactivate the ovarian niche, showing activated human follicle growth in mouse and xenografted human ovarian tissues.

Further, it was showed that BMDSCs reactivate and rescue human follicles in a prospective pilot study.

All other human studies have involved cell culture and use of the bone marrow-MSC fraction collected by iliac crest aspiration. By this approach, Gupta et al. reported a baby born to a 45- year-old premenopausal woman after autologous bone marrow-MSC therapy. In this study, bone marrow was aspirated from the posterior iliac crest,

and MSCs were instilled into both ovaries by laparoscopy. After 8 weeks, ovarian reserve markers AFC and AMH improved, so an IVF cycle was initiated. A healthy baby was born 11 months after treatment months, although this study only reports one case.

Different studies describe not only the regenerative potential of BMDSCs, but also a protective property, with a reduction of apoptosis in ovarian cells and lower germ cell DNA damage when combining chemotherapy with injection of BMDSCs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Journal of Medical Case Reports

CASE REPORT Open Access

Intraovarian injection of autologous human mesenchymal stem cells increases estrogen production and reduces menopausal symptoms in women with premature ovarian failure: two case reports and a review of the literature

Prosper Igboeli[1], Abdeljabar El Andalousi[2], Ujalla Sheikh[1], Hajra Takala[1], Amro ElSharoud[1], Ashley McHugh[1], Larisa Gavrilova-Jordan[3], Steven Levy[4] and Ayman Al-Hendy[1*]

Placenta MSc

The results of the related studeies provide evidence that women with ovarian dysfunction accompanied by aging may have the option to use hPD-MSCs to rejuvenate their ovaries and to attenuate the effects of menopause via the return of ovarian function.

Human Menstrual Blood-Derived Endometrial Cells (hMB-MSCs)

hMB-MSCs can differentiate into endothelial, neurocytic, cardiomyocytic, myocytic, cartilaginous, respiratory epithelial, pancreatic, adipocytic, hepatic, and osteogenic cells.

It was also demonstrated that hMB-MSCs could differentiate into ovarian tissue–like cells, and germ cells .

Adipose derived stromal cells (ADSCs).

- **Adipose tissue-derived mesenchymal stem cells (ADMSCs)** have also shown the ability to restore ovarian function, increasing the number of follicles after injection into the ovary in QT induced POF mice and rats
- An improvement in estradiol serum levels and an increase in the gestation rate

Autologous Cell Ovarian Transplantation (ASCOT)

Amniotic Epithelial Cell (AEC) and Amniotic Mesenchymal cells (AMSCs) Umbilical cord

Mesenchymal stem cells from human and murine amniotic fluid have shown the ability to survive and proliferate in the ovary and to rescue short-term fertility of mice with chemotherapy (QT)-induced POF after injection into the ovarian artery.

MSCs can also be obtained from the umbilical cord. The injection of **umbilical cord mesenchymal stem cells (UCMSCs)** into the tail vein allows improvement of the ovarian structure and ovarian function—at the hormonal and follicular level—in mice with POF induced by QT and in rats with natural ovarian aging

the recovery of ovarian function and fertility after UCMSCs transplantation occurs sooner when UCMSCs are injected directly into the ovarian artery

SOURCE

Fertility rescue and ovarian follicle growth promotion by bone marrow stem cell infusion

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Human BMDSCs were injected into mice with chemotherapy-induced ovarian damage and into immunodeficient mice xenografted with human cortex from poor-responder patients (PRs)

Our results raised the possibility that promoting ovarian angiogenesis by BMDSC infusion could be an alternative approach to improve follicular development in women with impaired ovarian function

Safety Issues

Reporting on the safety of stem cell therapy in ovarian insufficiency, serious considerations should be highlighted, especially in light of the lack of published evidence addressing any side effects related to this novel approach.

The most severe potential adverse effect is that unfortunately, intense cell proliferation events that occur following stem cell transplantation may induce malignant formation.

❑**Bone marrow derived stem cells (BMDSCs)** present an interesting alternative for transplantation in women with POI

- The possibility of obtaining a large number of BMDSCs, from an autologous source, by means of well-established clinical protocols—used for BM transplant after QT—makes them a valuable candidate

Administration Techniques

One is the stem cell administration technique although animal studies show that direct ovarian infusion is not required, human stem cells have been infused into one or both ovaries by various methods, such as direct injection via laparoscopy, transvaginal ultrasound-guided injection, intra-arterial catheterization of the ovarian artery or a combination of techniques.
Human stem cells have been infused into one or both ovaries by various methods, such as direct injection via laparoscopy, transvaginal ultrasound-guided injection, intra-arterial catheterization of the ovarian artery or a combination of techniques…..
This study, instead, had two branches: one arm received these cells by direct ovarian injection through laparoscopy, while the second arm had cells injected through de ovarian artery.

Effectiveness

Considering the aforementioned, it is of added value to determine both the appropriate dose and the specific administration time following stem cell harvesting, in order to achieve a balance between safety and efficiency.

The appropriate dose and specific administration time following stem cell harvesting, the appropriate administration method, the duration of the recovery period and the potential treatment replication are all issues of value that merit further investigation.

Complications

Several recent studies have raised concerns about potential side effects of exogenous stem cells after transplantation, such as tumor formation and neoplastic transformation.
Although MSCs have proven to be a safer source of stem cells compared to other types of pluripotent stem cells they carry an inherent risk of tumor-like mass formation recent studies have raised concerns about potential side effects of exogenous stem cells after transplantation, such as tumor formation and neoplastic transformation. Although MSCs have proven to be a safer source of stem cells compared to other types of pluripotent stem cells they carry an inherent risk of tumor-like mass formation.

It is well documented that long-term cultured mesenchymal stem cells could induce tumorigenesis and metastasis. Following stem cells, isolation from their source of origin, in vitro expansion of cell population is typically required to achieve a clinically suitable grade of stem cells. However, stem cells at higher passages could lead to malignant cell transformation.

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Journal of Ovarian Research

RESEARCH Open Access

Evaluation of safety, feasibility and efficacy of intra-ovarian transplantation of autologous adipose derived mesenchymal stromal cells in idiopathic premature ovarian failure patients: non-randomized clinical trial, phase I, first in human

M. Mashayekhi[1], E. Mirzadeh[2], Z. Chekini[1], F. Ahmadi[3], P. Eftekhari-Yazdi[4], S. Vesali[5], T. Madani[1*] and N. Aghdami[2*]

The primary objective of the current study was to evaluate the safety of ADSCs transplantation. Participants were followed for early-onset possible side effects such as bacteremia, sepsis, PID, anaphylactic shock, and hematoma from the first 24 h and during the first week because of the transplantation procedures.

The patients remained in follow up for the second week, and for 1, 2, 3, 6, and 12 months after the transplantation to evaluate safety and effectiveness, and any secondary complications, physical examination and vaginal ultrasonography.

Secondary objectives included and the effects of ADSCs transplantation on the resumption of menstruation, hormones level (FSH and anti-Müllerian hormone [AMH]), ovarian function (AFC and ovary volume by ultrasonography evaluation).

This is particularly true in cases of idiopathic POF, which comprises pproximately 90% of POF cases.

Edessy et al. (2016)reported the first autologous bone marrow stem cell transplantation via laparoscopy into the ovaries as treatment for idiopathic POF. The results showed recovered menstruation in two cases (20%) 3 months after the transplantation. One case (10%) became pregnant and delivered the first baby from this therapeutic procedure.

Conclusion

This study showed that clinical applications of ADSCs therapy are safe more than 1 year and feasible and efficacy (decrease FSH and resumption menstrual). The results for each cell count were not significantly different, and some variables showed favorable results after transplantation with the 5 × 106 dose of ADSCs. We suggest that to achieve the best results, the 5 × 106 ADSCs can be transplanted two times and bilaterally into the ovaries because they provide a rich microenvironment for both ovaries as well as had cost-benefit. However, further studies with larger numbers of patient in different clinical trial stage

Journal of

Conclusions: Our study reveals promising improvement of premature ovarian failure–related clinical manifestations in two patients after intraovarian autologous bone marrow–derived mesenchymal stem cells engraftment. These early observations call for additional assessment and further development of intraovarian bone marrow–derived mesenchymal stem cell injection for possible treatment of patients with premature ovarian failure.

production and reduces menopausal symptoms in women with premature ovarian failure: two case reports and a review of the literature

Prosper Igboeli[1], Abdeljabar El Andaloussi[2], Ujalla Sheikh[1], Hajra Takala[1], Amro ElSharoud[1], Ashley McHugh[1], Larisa Gavrilova-Jordan[3], Steven Levy[4] and Ayman Al-Hendy[1*]

ment. In addition, no complications or safety concerns were reported in our study. More studies are needed to evaluate this approach, and we will also continue reporting our ongoing clinical trial.

Original Article

Safety of Intraovarian Injection of Human Mesenchymal Stem Cells in a Premature Ovarian Insufficiency Mouse Model

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Though the therapeutic potential of MSCs in various disease conditions is well documented, safety concerns in using allogeneic MSC as a biological drug remain. Several Though the therapeutic potential of MSCs in various disease conditions is well documented, safety concerns in using allogenic MSC as a biological drug remain.

In this study, we reported that the injected hBM-MSCs stay in the ovary and do not migrate to other tissues.

Safety of Intraovarian Injection of Human Mesenchymal Stem Cells in a Premature Ovarian Insufficiency Mouse Model

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The number of injected hBM-MSCs decreased by more than 50% within 2 weeks and disappeared entirely in most animals within 4 weeks after injection.

In addition, while hBM-MSC treatment restored fertility, the effect diminished by 78 days following cell transplantation.

Moreover, we revealed a lack of genetic integration from the injected cells in the offspring of treated mice, and that hBM-MSC treatment did not affect the postnatal growth of the offspring.

Taken together, this study provides further evidence that intraovarian injection of hBM-MSCs may be a safe therapy for restoring fertility in POI,