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Advances in mesenchymal stromal/stem cell therapy for non-obstructive azoospermia: a comprehensive mini-review

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ABSTRACT

Azoospermia, characterized by the absence of sperm in semen, poses a significant challenge to male fertility. Mesenchymal stromal/stem cell (MSC) therapy has emerged as a promising approach for treating azoospermia by promoting spermatogenesis and restoring fertility. MSCs possess the ability to differentiate into male germ cells and create a favorable microenvironment for spermatogenesis through the secretion of growth factors and cytokines. Preclinical studies have shown encouraging results, with improved testicular histology, sperm production, and fertility outcomes in animal models of azoospermia. Limited clinical studies in humans have also demonstrated the potential of MSC therapy in restoring spermatogenesis. However, challenges such as standardization of MSC isolation, characterization, and administration protocols, as well as the need for long-term safety and efficacy data, remain to be addressed. Despite these challenges, MSC therapy holds great promise for the treatment of azoospermia and warrants further research to optimize its use in clinical practice.

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Abbreviations

MSC, Mesenchymal stromal/stem cell; OA, obstructive azoospermia; TESE, Testicular sperm; extraction; ART, assisted reproductive techniques; NOA, non-obstructive azoospermia

Introduction

Azoospermia, defined as the absence of sperm in ejaculated semen, presents a significant hurdle to male fertility affecting approximately 1% of the male population (1). It is classified into two main categories: obstructive azoospermia (OA) and non-obstructive azoospermia (NOA) (2). OA is characterized by physical blockages that prevent sperm from being ejaculated (3), while NOA results from testicular dysfunction leading to impaired sperm production (4).

Treatment options for NOA are limited, and conventional methods such as hormonal therapy, surgical retrieval of sperm (testicular sperm extraction, TESE), and assisted reproductive techniques (ART) are often used (5). However, these methods have varying success rates and may not always result in successful conception.

Cell therapy, particularly using mesenchymal stromal/stem cells (MSCs), has emerged as a promising alternative for treating NOA (6). MSCs offer several advantages, including their ability to differentiate into various cell types, including germ cells, and their immunomodulatory and tissue repair properties (7). These characteristics make MSCs an attractive candidate for restoring spermatogenesis in NOA patients (7).

MSC therapy has shown promising results in preclinical studies, with the potential to restore spermatogenesis and improve fertility outcomes in animal models of NOA (7). Additionally, limited clinical studies in humans have demonstrated the safety and efficacy of MSC therapy for NOA (8). However, further research is needed to optimize MSC therapy protocols, establish long-term safety and efficacy, and address regulatory challenges before it can be widely adopted as a standard treatment for NOA.

The main aim of this mini-review is to provide an overview of the potential of MSC therapy for the treatment of azoospermia, with a focus on NOA. The review aims to discuss the different types of azoospermia, the limitations of current treatment options for NOA, and the potential of MSC therapy as a novel and promising approach. It also aims to highlight the importance of MSC therapy in restoring spermatogenesis and improving fertility outcomes in NOA patients, based on both preclinical and limited clinical studies.

The review may also discuss the challenges and future directions of MSC therapy for azoospermia, emphasizing the need for further research to optimize its use in clinical practice.

MSCs in NOA Therapy

MSCs are multipotent stem cells with the ability to differentiate into various cell types, including germ cells (9). They possess immunomodulatory properties and can promote tissue repair and regeneration, making them an attractive candidate for treating azoospermia (10).

MSCs can differentiate into male germ cells, such as spermatogonia, spermatocytes, and spermatids, offering a potential source for replenishing spermatozoa (11). MSCs can differentiate into spermatogonia, spermatocytes, and even mature sperm cells under certain conditions (7). This differentiation process can replenish the pool of germ cells in the testes, which is essential for spermatogenesis and ultimately sperm production (12).

Additionally, MSCs secrete growth factors, cytokines, and extracellular vesicles, which can create a favorable microenvironment for spermatogenesis (13). MSCs have strong immunomodulatory properties, meaning they can regulate the immune response in the testicular microenvironment (14). In conditions such as NOA, there is often an inflammatory response or immune dysfunction in the testes, which can impair spermatogenesis (4). MSCs can modulate this immune response, reducing inflammation and creating a more favorable environment for spermatogenesis to occur (14). MSCs secrete various growth factors, cytokines, and extracellular vesicles that promote tissue repair and regeneration (15). In the context of azoospermia, MSCs can stimulate the repair of damaged testicular tissue, which is crucial for restoring normal spermatogenesis (16). These factors can also enhance the survival and proliferation of existing germ cells, further supporting sperm production (17).

MSCs can create a supportive microenvironment within the testes through the secretion of factors that promote cell survival, proliferation, and differentiation (18). This microenvironment is essential for the proper functioning of germ cells and spermatogenesis (19). By creating such a microenvironment, MSCs can support and enhance the natural process of sperm production (7).

Therefore, MSCs play a crucial role in the regeneration of testicular tissue and the treatment of azoospermia. Their ability to differentiate into germ cells, modulate the immune response, promote tissue repair, and create a favorable microenvironment makes them a promising therapeutic option for restoring spermatogenesis and fertility in men with azoospermia.

Preclinical Studies in NOA Therapy

Several preclinical studies have investigated the potential of MSC therapy in restoring spermatogenesis in animal models of azoospermia, including NOA (7). These studies have shown promising results, with improvements in testicular histology, sperm production, and fertility outcomes following MSC administration.

Studies in mouse models of NOA have demonstrated that MSCs can differentiate into germ cells and restore spermatogenesis (20). These studies have shown improvements in testicular function and sperm parameters after MSC therapy (21). Rat (17, 22), hamster (16) and Guinea pig (23) models have also been used to study the effects of MSC therapy on NOA. These studies have shown similar outcomes to those in mice, with MSCs promoting spermatogenesis and improving fertility in NOA rats.

MSC therapy has been shown to improve testicular histology in animal models of NOA (24). This includes increased numbers of germ cells, improved seminiferous tubule structure, and reduced fibrosis or inflammation (24).

Animal studies have demonstrated that MSC therapy can increase sperm production in NOA models (25). This is often accompanied by improvements in sperm quality and motility (26).

MSC therapy has been associated with enhanced fertility outcomes in animal models of NOA. This includes increased pregnancy rates and litter sizes in treated animals compared to untreated controls (7).

Therefore, preclinical studies in various animal models of NOA have provided valuable insights into the potential of MSC therapy for restoring spermatogenesis and improving fertility outcomes. These studies have shown that MSCs can improve testicular histology, increase sperm production, and enhance fertility in animal models of NOA, highlighting the promise of MSC therapy as a potential treatment for NOA in humans.

Clinical Studies in NOA Therapy

Limited clinical studies have explored the use of MSC therapy for azoospermia in humans (8, 25, 27). While initial results are promising, larger, well-controlled trials are needed to establish the safety and efficacy of MSCs in treating azoospermia in men. Notably, recent clinical trials have provided further insights into the potential of MSCs in NOA treatment.

One such study by Alhefnawy et al., evaluated the effect of local intratesticular injection of MSCs in inducing spermatogenesis in NOA patients. Their findings revealed that 20.7% of patients exhibited sperm in semen post-treatment, accompanied by significant improvements in hormonal profiles and sexual function (25, 27). This study highlights the potential of MSC therapy as a novel approach for refractory NOA cases.

Similarly, Zhankina et al. conducted a Phase I clinical trial utilizing autologous BM-MSCs for NOA treatment. Their results demonstrated significant improvements in sperm concentration, hormonal profiles, and fertility outcomes following BM-MSC autotransplantation via microTESE, without complications. Notably, successful outcomes were observed in 22.5% of patients with secondary infertility, underscoring the broad applicability of this approach (8).

These clinical trials provide valuable insights into the feasibility and safety of MSC therapy in NOA treatment. However, further research with larger sample sizes and rigorous methodologies is warranted to establish the long-term safety and efficacy of MSC-based interventions in azoospermia management.

Challenges and Future Directions

Challenges such as standardization of MSC isolation, characterization, and administration protocols need to be addressed. Furthermore, long-term safety and efficacy data, as well as regulatory approvals, are essential before MSC therapy can be widely adopted for azoospermia treatment.

Conclusion

Azoospermia, particularly NOA, presents a significant challenge to male fertility treatment. Current therapies, including hormonal treatments, surgical sperm retrieval, and assisted reproductive techniques, have limitations and varying success rates. MSC therapy has emerged as a promising alternative for NOA treatment, offering potential benefits in restoring spermatogenesis and improving fertility outcomes.

Preclinical studies using animal models of NOA have demonstrated that MSC therapy can promote the regeneration of testicular tissue, improve testicular histology, increase sperm production, and enhance fertility outcomes. These studies have shown that MSCs can differentiate into germ cells, modulate the immune response, promote tissue repair and regeneration, and create a supportive microenvironment for spermatogenesis.

Although limited, clinical studies in humans have also shown promising results, indicating the safety and efficacy of MSC therapy for NOA. However, challenges such as standardization of protocols, long-term safety and efficacy data, and regulatory approvals need to be addressed before MSC therapy can be widely adopted as a standard treatment for NOA.

Therefore, MSC therapy holds great promise for the treatment of NOA by addressing the underlying causes of impaired spermatogenesis and offering a potential cure for azoospermia. Further research is warranted to optimize MSC therapy protocols, establish its long-term safety and efficacy, and overcome regulatory challenges, ultimately providing a novel and effective treatment option for NOA patients.

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Conflicts of interest/Competing interests

The authors declare no conflict of interest.

Authors' contributions

F.R. designed the study concept and drafted the manuscript. N.M.M. collected data and drafted the manuscript. A.T. designed the study concept, reviewed and revised the manuscript.

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