Chapter 11
Cell-Based Therapies in Clinical Pain Management

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Abstract Development of novel therapies is required to transform care for chronic and refractory pain due to degenerative and neuropathic conditions. Mesenchymal stem cell (MSC)-based therapies are supported by strong biological rationale based upon the remarkable immunomodulatory and analgesic effects of MSCs shown in pre-clinical studies. Such therapies are not only feasible but also are becoming a reality in clinical practice for a wide range of immunologically related diseases. In the field of pain medicine, there is a growing body of literature that reports promising results from randomized clinical trials for joint pain and prospective studies for neuropathic pain. These clinical investigations demonstrate that MSC therapies are not only safe but also efficacious for their respective indications. Further investigations are required to translate research findings to clinical practice. The key to increasing the scientific rigor and success of future clinical trials is to use refined standardized research protocols and cell quality control standards that take into account of factors such as appropriate selection of patients, source of cells, donors of cells, methods of cell processing, route of administration, and number of transplantations (doses). In this chapter, I will focus on these critical aspects of clinical investigation of MSC-based therapies.

Keywords Mesenchymal stem cells (MSCs) · Autologous MSCs · Allogeneic MSCs · Chronic pain · Neuropathic pain · Degenerative joint pain · Discogenic pain · Chronic low back pain · Osteoarthritis · Rheumatoid arthritis · Randomized clinical trials (RCT) · Prospective studies, Systematic reviews

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11.1 Introduction

Managing chronic pain from degenerative and neuropathic conditions is one of the greatest challenges in pain medicine (Cheng 2019a, b; Cheng et al. 2020). Patients with such chronic pain conditions frequently fail to respond to the current treatment continuum (Cheng et al. 2022), ranging from physical, cognitive-behavioral, pharmacological (Xu et al. 2016), interventional (Cheng et al. 2019; Shin and Cheng 2021; Xu et al. 2017, 2021, 2022), to surgical approaches (Cheng et al. 2022; Rogers et al. 2021; Xu et al. 2021) (Fig. 11.1). Thus, novel and more efficacious treatment strategies are urgently needed to relieve the burden of pain, suffering, and disability. Regenerative medicine is a rapidly growing area of research and clinical applications (Buchheit et al. 2020). Recent studies suggest that regenerative therapies may significantly improve symptoms and distinctly modify disease processes of chronic pain through neuroimmune-modulatory and analgesic effects of regenerative agents. In this chapter, we focus on clinical investigations of MSC-based therapies in the management of chronic pain. Preclinical studies of mesenchymal stem cell (MSC) therapies are discussed in Chap. 10. Other regenerative approaches through platelet rich plasma (PRP) and autologous conditioned serum (ACS) are discussed in Chap. 12. Cell-free therapies employing exosomes or gene therapies are active areas of research but are beyond the scope of this chapter.

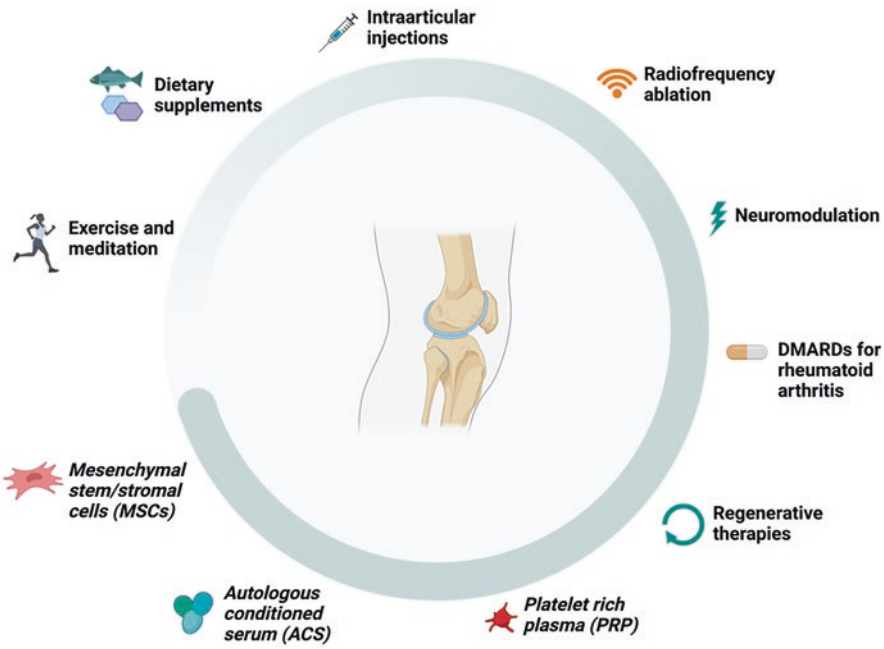

Fig. 11.1 Continuum of joint pain treatment. (Modified from Cheng et al. 2022, Elsevier)

The biological rationale for MSC therapy is multifold and has been discussed extensively in Chap. 10. Briefly, recent studies demonstrate that autoimmune processes and neuroimmune interactions play central roles in the pathogenesis of chronic pain (Birklein et al. 2014; Cuhadar et al. 2019; David Clark et al. 2018; Goebel and Blaes 2013; Helyes et al. 2019; Prasad and Chakravarthy 2021; Tékus et al. 2014; Uçeyler et al. 2007). MSCs, which are present in the perivascular space of nearly all tissues (Lin et al. 2014; Spees et al. 2016), are capable of profoundly modulating neuroimmune functions through multiple mechanisms, including direct cell-to-cell contact, paracrine secretion of cytokines (e.g., TGF-β1, IL-10), chemokines, and growth factors, homing of released exosomes or microvesicles that contain immunoregulatory molecules, and mitochondrial trafficking via tunneling nanotubes (Najar et al. 2016; Song et al. 2020; Spees et al. 2016). Remarkably, it has been demonstrated that apoptotic, metabolically inactivated, or even fragmented MSCs possess immunomodulatory capabilities (Chang et al. 2012; Gonçalves et al. 2017; Luk et al. 2016). As an emerging therapy in pain management (Buchheit et al. 2020), MSC transplantation has shown promise in preclinical studies to treat neuropathic pain (NP) (Chen et al. 2015; Hosseini et al. 2015; Liu et al. 2017), opioid tolerance (Cheng 2018; Hua et al. 2016; Li et al. 2018), and chronic pain due to degenerative musculoskeletal diseases (Centeno et al. 2017; Chakravarthy et al. 2017; Kim et al. 2022; Vega et al. 2015).

Translating MSC-based therapies to clinical practice is not only feasible (Buchheit et al. 2020; Law et al. 2019) but is also a current reality with recent breakthroughs (Levy et al. 2020). The first allogeneic stem cell therapy using a product of adipose-derived hMSCs (Alofisel) has been approved by the European Medicines Agency (EMA) for use in clinical practice in the European Union to treat complex perianal fistulas in Crohn's disease based upon a successful Phase III trial (Panés et al. 2016). In addition to Alofisel, there are 10 globally approved MSC therapies and products to treat a variety of diseases such as graft versus host disease (GvHD) (Canada, New Zealand, and Japan), knee articular cartilage defects (South Korea), spinal cord injury (Japan), critical limb ischemia (India), and acute myocardial infarction (South Korea). Interestingly, in a randomized controlled trial, it is recently demonstrated that infusion of UC-MSCs dramatically improved survival in patients with COVID-19 acute respiratory distress syndrome (Lanzoni et al. 2021). Currently, the use of hMSCs for various diseases is being investigated in nearly 1000 clinical trials (Jayaraman et al. 2021; Kabat et al. 2020), among which about 100 are designed for immune-mediated disorders, such as rheumatoid arthritis (Lopez-Santalla et al. 2020), multiple sclerosis (Zhou et al. 2019), and diabetes (Bhansali et al. 2017; Cai et al. 2016). A significant and consistent finding from published clinical trials is that MSC therapy is not only safe, but also efficacious in improving clinical outcomes in a number of diseases (Saeedi et al. 2019).

11.2 Factors That Determine Clinical Outcomes

11.2.1 Quality Control of MSCs

Quality control of human MSCs is of paramount importance for successful application in clinical investigations and clinical practice. There are established protocols regarding the raw materials, equipment, and processes of generating hMSCs under current good manufacture practice (cGMP). Important considerations include the source of MSCs (bone marrow vs. adipose tissue vs. umbilical cord tissue), autologous vs. allogeneic, age and health status of donors, number of cell passages, and absence of biological and other sources of contamination (Zaim et al. 2012). Early (2nd–3rd) passages of allogeneic hMSCs that meet lot release criteria are typically used to minimize variability and ensure a streamlined and safe supply at low cost (Jayaraman et al. 2021; Pittenger et al. 2019).

Many patients with chronic pain seek experimental therapies after failure of response to available therapies. To fill this void, clinics have emerged to offer "stem cell" therapy using unproven products and methods. This development has led the FDA to issue a Consumer Alert about concerns that patients seeking remedies may be misled by information about products, which place patients at risk (July 22, 2020, FDA).

11.2.2 Transplantation Protocols

Outcomes of clinical investigations of cell-based therapies are determined particular key factors of experimental design, including patient selection, sources of cells, donors of cells, processing methods of cells, route of application, and the number of transplantations (doses). Investigators must take into consideration these critical factors to ensure scientific rigor and the success of clinical investigations. Patient selection through inclusion and exclusion criteria is based upon indications of the therapy and patient characteristics that include biopsychosocial profiling and responsiveness to previous treatments.

Autologous bone marrow aspirate or adipose tissue aspirate containing MSCs are used in many cell-based studies with minimal manipulation of the cells (Durand and Zubair 2022) (Fig. 11.2). Examples of this type of use of autologous MSCs include studies to treat trigeminal nerve neuropathic pain (Vickers et al. 2014), pudendal neuralgia (Venturi et al. 2015), shoulder joint pain (Dwyer et al. 2021), and discogenic pain (Pettine et al. 2015). These types of studies typically lack adequate cell quality control measures and may be unclear about the number, vitality, and purity of cells. Furthermore, the sources of the cells used are cost-prohibitive with limited cell dosages, high donor variability, and potentially biological incompatibility issues. The advantage of using autologous cells, however, is that their use is more permissive under current FDA regulations.

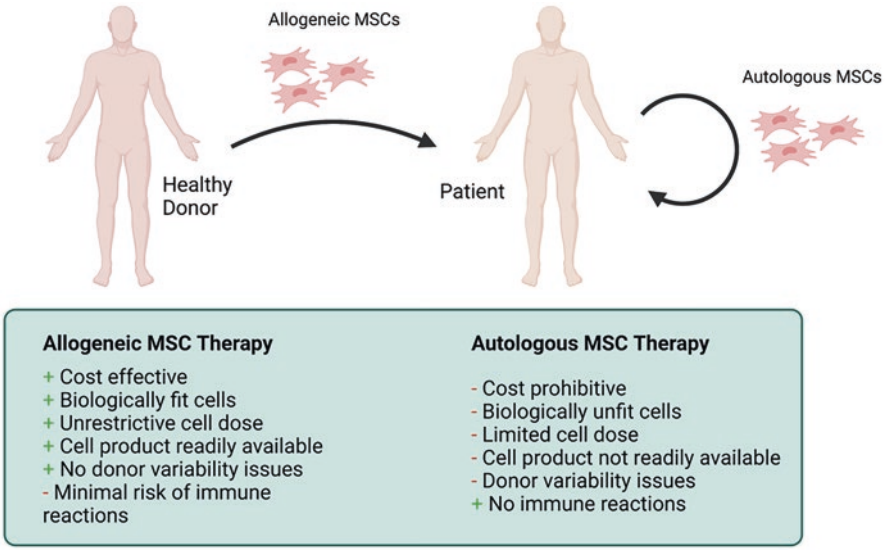

Fig. 11.2 Pros and cons of autologous vs. allogeneic MSCs. (Modified from Durand and Zubair 2022, Elsevier)

Allogeneic MSCs, in contrast, are typically from young and healthy donors who are screened with strict tests and criteria (Durand and Zubair 2022). Cells are processed and multiplied through cell culture under cGMP conditions with comprehensive quality control measures and criteria. Most clinical trials utilize clinical grade BM-MSCs, AD-MSCs, or UC-MSCs that are provided by off-the-shelf and ready-to-use packages. Such cells can be used either directly after thawing or alternatively after subsequent culture so that fresh cells are utilized. The advantages of using allogeneic MSCs include optimal selection of high-quality cells, minimal variability between cell products, cost-effectiveness, and streamlined and safe supply to multiple centers for clinical investigation or application.

A variety of routes of transplantation have been utilized in clinical investigation, including intravenous, intrathecal, intraarticular, intradiscal, subcutaneous, and site of injury applications. The route of application chosen is primarily dictated by the pathophysiology of the clinical indication under investigation. For example, intraarticular injections are used in almost all trials for knee osteoarthritis (OA) as a result of localized degenerative changes in the joint while intravenous injections are most commonly used in trials for knee rheumatoid arthritis (RA) as a result of the systemic autoimmune disorder (Hwang et al. 2021). Either a single injection or repeated multiple dose injections may be studied in clinical trials for sustained therapeutic effects.

11.3 Evidence from Clinical Investigations of MSC Therapy for Degenerative Joint Pain

11.3.1 Knee and Shoulder Osteoarthritis

Osteoarthritis affects more than 46 million Americans and is a major cause of disability. Stem cell therapy for osteoarthritis is an area of intensive research in preclinical and clinical settings (Fig. 11.3) (Cheng 2018). A substantial number of randomized clinical trials (RCTs) on the management of knee OA with stem cells have been reported and 19 meta-analyses of clinical studies were published from January 2020 to July 2021. An independent, systematic review of the literature yielded a total of 183 studies, of which 33 were randomized clinical trials, including a total of 6860 patients with knee OA (Schmitz et al. 2022). The review emphasized that it is important to recognize methodological limitations, interpret the results, and draw conclusions from systematic review and meta-analyses.

Intra-articular injections of MSCs may improve pain and functionality. A systematic review of intra-articular injections of MSCs without adjuvant therapies for knee OA included a total of 19 studies on 440 knees treated (Tan et al. 2021). All

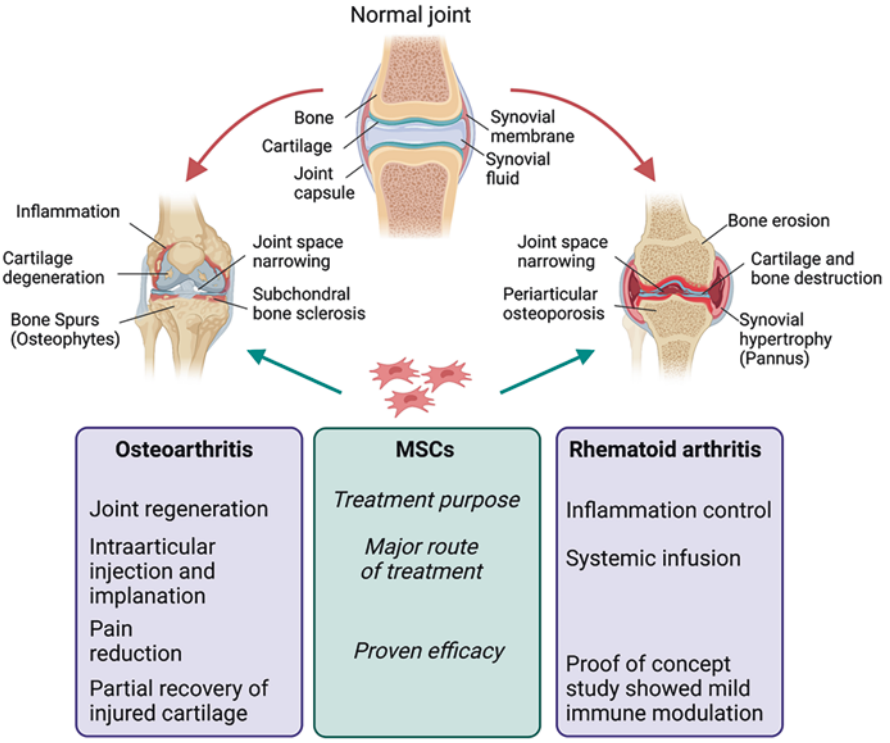

Fig. 11.3 MSCs for OA and RA. (Modified from Hwang et al. 2021)

studies reported an improvement in visual analogue scale (VAS) pain scores and functional outcome measures such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Osteoarthritis Outcome Score following intervention. The review concluded that intra-articular injections of MSCs, without adjuvant therapies, can improve pain and function for osteoarthritis. Significantly better outcomes were obtained with the use of bone marrow-derived MSCs (BM-MSCs) as compared with adipose-derived MSCs (AD-MSCs) and with the use of cultured MSCs as opposed to uncultured MSCs.

There are notable inconsistencies in reported outcomes. A systematic review and meta-analysis of 10 RCTs on MSCs for knee arthritis included studies in 335 patients (Ma et al. 2020). MSC therapy yielded beneficial effects at 6, 12, and 24 months, with significant improvement in VAS, WOMAC and low rates of adverse events. This meta-analysis showed that both BM-MSCs and AD-MSCs had a great application potential in the treatment of knee OA. AD-MSCs tended to be superior to BM-MSCs according to the limited clinical evidence available. However, a similar review of 13 RCTs found that, compared with placebo, there was no significant difference in VAS for pain, WOMAC pain score, WOMAC function score, or WOMAC stiffness score for MSCs (Dai et al. 2021). Therefore, caution must be taken when clinicians interpret the results of meta-analyses of clinical studies on the management of knee OA with stem cells (Schmitz et al. 2022).

The dosage or number of cells administered to a patient, in addition to the source of cells, may impact outcomes. A systematic review and meta-analysis focused on the effects of cell count and included 14 studies involving 564 patients (Muthu et al. 2022). The authors categorized the studies based on the MSC count into four groups, namely less than 1×10^7 cells, between 1–5 $\times 10^7$cells, between 5–10 $\times 10^7$cells, and greater than 10×10^7 cells. They noted incremental decreases in the VAS with increasing dosages of MSCs at 12 months and 24 months and incremental improvement in the WOMAC, KOOS with increasing dosage of MSCs at 12 months respectively. They did not find any significant increase in the adverse events with increased dosage of MSCs in any of the groups compared. It was concluded that treatment with between 5–10 $\times 10^7$ cells showed consistent and significant improvement in pain and functional outcomes compared to the other treatment groups. Hence, a cell count between 5–10 $\times 10^7$ MSCs is recommended for the target site to obtain superior benefits from the procedure.

A recent pilot RCT compared the efficacy of a single, intra-articular, nonconcentrated bone marrow aspirate (BMA) injection in comparison to cortisone for the treatment of glenohumeral joint OA-related shoulder pain (Dwyer et al. 2021). The study included 25 shoulders injections of 22 patients who completed baseline and 12 month patient-reported outcome measures (12 shoulders received cortisone, 13 shoulders received BMA). In the BMA group, a significant improvement was seen in Western Ontario Osteoarthritis of the Shoulder (WOOS) index ($p = 0.002$), the QuickDASH (11 items to measure physical function and symptoms in people with any or multiple musculoskeletal disorders of the upper limb), and the EQ-5D-5L pain dimension between baseline and 12 months. No significant difference was seen for any outcome in the cortisone group between baseline and 12 months. A

significant difference in changes in scores was seen in the QuickDASH and the EQ-5D-5L pain scores and the EQ-5D-5L health scores in favor of BMA. It was concluded that patients with glenohumeral joint OA treated with BMA have superior changes in the QuickDASH and EQ-5D-5L pain and health scores at 12 months post-injection when compared to patients treated with cortisone.

These studies strongly suggest that MSC therapy may provide pain relief and functional improvement in patients with joint pain due to osteoarthritis. Further studies with more rigorous designs should take into account the cell types, cell counts, cell quality, and means of delivery, as well as patient characteristics such as age and stages of disease.

11.3.2 Intervertebral Discogenic Pain

Percutaneously delivered MSC therapy has been proposed as a potential means to holistically ameliorate discogenic low back pain through three mechanisms: mitigation of primary nociceptive disc pain, reduction or reversal of the catabolic metabolism, and restoration of disc tissue.

In an open label pilot study (Pettine et al. 2015), 26 patients (median age 40 years; range 18–61) received autologous bone marrow concentrate (BMC) disc injections (13 one level, 13 two levels). Approximately 1 ml of BMC was analyzed for total nucleated cell (TNC) content, colony-forming unit-fibroblast (CFU-F) frequency, differentiation potential, and phenotype characterization. The average Oswestry disability index (ODI) and VAS scores were reduced to 22.8 and 29.2 at 3 months, 24.4 and 26.3 at 6 months, and 25.0 and 33.2 at 12 months, respectively ($p \leq 0.0001$). Eight of twenty patients had improved disc degenerative severity by one modified Pfirrmann grade on MRI at 1 year. The average BMC contained 121×10^6 TNC/ml with 2713 CFU-F/ml (synonymous with MSCs). Although all subjects presented a substantial reduction in pain, patients receiving greater than 2000 CFU-F/ml experienced a significantly faster and greater reduction in ODI and VAS. Subjects younger than 40 years of age experienced an average pain reduction of 69.5% for ODI ($p = 0.03$) and 70.6% VAS score ($p = 0.01$) at 12 months. This study provides evidence of the safety and feasibility for the nonsurgical treatment of DDD with autologous BMC and indicates an effect of mesenchymal cell concentration on discogenic pain reduction. Follow-up studies further confirmed these findings in the non-surgical treatment of discogenic pain with autologous BMC, with durable pain relief (71% VAS reduction) and ODI improvements (>64%) through two years (Pettine et al. 2016) and three years (Pettine et al. 2017).

A systematic review of 7 studies involving 97 patients found significant improvements in VAS (66.0–20.9 mm, $p < 0.001$) and ODI (44.4–19.1, $p < 0.001$) after the intradiscal BMC injection. It was concluded that intradiscal injection of BMC for lumbar disc degeneration resulted in statistically and clinically significant improvements in VAS and ODI with low re-injection and complication rates (Hirase et al. 2020). More recently, we systematically reviewed the effectiveness of intradiscal

biologic treatments for discogenic low back pain (Schneider et al. 2022). It was found that, for mesenchymal stem cells, the aggregate success rate (≥50% improvement) at six months is 53.5% (95% Confidence Interval: 38.6–68.4%), though using worst-case analysis this rate decreased to 40.7% (95% Confidence Interval: 28.1–53.2%). Also, ≥30% functional improvement was achieved in 74.3% of cases (95% Confidence Interval: 59.8–88.7%) at 6 months but using worst-case analysis, this rate decreased to 44.1% (95% Confidence Interval: 28.1–53.2%). Thus, preliminary observation supports the use of intradiscal biologic agents for the treatment of discogenic low back pain.

11.4 Evidence from Clinical Investigations of MSC Therapy for Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease, which affects the lining of the synovial joints causing inflammation, loss of mobility, erosion of joints, and stiffness and pain (Fig. 11.3) (Hwang et al. 2021). A key component for the pathogenesis of RA is abnormal immune responses against the synovium. Progression of RA is characterized by dysfunction of innate and adaptive immunity, including dysregulated cytokine networks and immune complex-mediated complement activation. Current treatments to modulate the altered immune responses include corticosteroids, antirheumatic drugs, and biological agents, which may cause adverse effects to a significant number of RA patients. Additionally, some RA patients are resistant to these therapies. In recent years, MSC-based therapies have been proposed as a novel and promising therapeutic approach in the treatment of RA (Lopez-Santalla et al. 2020). To date, nearly one hundred studies in animal RA models have shown promising results for clinical application. Proof-of-concept clinical studies have demonstrated a satisfactory safety profile for RA treatment with MSC therapy.

Clinical trial registrations in RA patients with MSC therapy have increased linearly since 2011 and reached a plateau in 2018 (Lopez-Santalla et al. 2020). In general, toxicity or adverse effects have not been found in any of the RA clinical trials conducted. Not enough sufficient data on efficacy has been obtained from the completed studies, most likely because these studies were underpowered. Also, the large majority of RA patients enrolled in these studies were refractory to conventional RA treatments with a long history of disease. Given the excellent safety profile of MSC-based therapy, there are eight clinical trials using MSC-based therapy that are registered and active in "clinicaltrials.gov" where MSC therapy at early stages of RA are being explored. For better comparisons of results among clinical trials, an improvement in the standardization of treatment protocols is needed in terms of sources of MSCs, MHC contexts, manufacturing protocols, routes of delivery, cell dosing (cell number), and systematic analysis of the results. Additionally, appropriate selection of patients who are most likely to respond to the therapy will benefit the clinical application of MSC therapy for RA.

11.5 Evidence from Clinical Investigation of MSC Therapy for Neuropathic Pain

Many neuropathic pain conditions are debilitating and difficult to treat. Managing neuropathic pain is one of the most significant challenges in clinical pain. Application of MSC therapy is limited to a few prospective case series, in which autologous adipose or bone marrow aspirates containing "MSCs" were injected locally or intrathecally, and patients reported a significant reduction of neuropathic pain caused by injuries of the trigeminal nerve (Vickers et al. 2014), the pudendal nerve (Venturi et al. 2015), or the spinal cord (Vaquero et al. 2018). While intriguing, these clinical reports are preliminary due to a lack of control groups and small sample sizes.

Trigeminal neuropathic pain is a debilitating condition that affects the face. It is often refractory to pharmacological or procedural treatment. In a case series (Vickers et al. 2014), 10 female patients with symptoms of neuropathic trigeminal pain were prospectively treated with local injections into the pain field with the stromal vascular fraction of lipoaspirate that contained 33 million to 162 million autologous "MSCs" with a cell viability of 62–91%. There were no systemic or local tissue side effects from the stem cell therapy (n = 41 oral and facial injection sites). At 6 months, 5 out of 9 subjects had reductions in both pain intensity scores and use of anti-neuropathic medication. Their mean numeric rating scale (NRS) pain scores were also significantly reduced from 7.5 at the pre-treatment timepoint to 4.3 at 6 months. Thus, this preliminary open-labeled study is promising, showing that administration of autologous stem cells is a safe and well-tolerated intervention for neuropathic trigeminal pain and significantly reduced pain intensity at 6 months.

Pudendal neuralgia is also a difficult-to-treat condition that affects the perineal area. A case series of 15 female patients with pudendal neuralgia were prospectively treated with transperineal injections of autologous adipose tissue with MSCs along the Alcock's canal (Venturi et al. 2015). Twelve patients completed the follow-up protocol. There were no complications. Two patients had no pain improvement and continued to use analgesic drugs. The mean VAS pain score significantly reduced from 8.1 pre-treatment to 3.3 at 12 months while the health quality measure SF36 significantly improve from 85.0 pre-treatment to 75.5 at 12 months. It was concluded that this new treatment is readily administered, carries low risk of complications, and provides significant improvement of symptoms.

Spinal cord injury (SCI)-related neuropathic pain represents a significant cause of decreased quality of life. In a prospective study (Vaquero et al. 2018), 10 patients suffering from chronic SCI received 100 million BM-MSCs into the subarachnoid space by lumbar puncture during the first month of the study. This procedure was repeated at months 4 and 7 of the study, reaching a total dose of 300 million cells. The mean VAS pain score reduced significantly from 5.5 pre-treatment to 1.5 at 10 months post-treatment. This study supports the use of intrathecal administration of autologous MSCs for the treatment of neuropathic pain in patients with SCI.

11.6 Summary

MSC therapy has shown its safety and efficacy in studies ranging from RCTs for joint pain to prospective case series for neuropathic pain. MSC therapy has shown potential for treating both OA and RA with reduced pain, improved joint function, and enhanced overall life satisfaction in patients, although osteoarthritis (OA) patients had more promising results compared to rheumatoid arthritis (RA) patients. Clinical trials on OA and RA demonstrate that MSC therapy is a safe treatment option without serious adverse events. For neuropathic pain, MSC therapy has gained preliminary data that support the safety and efficacy even in patients with the most difficult-to-treat conditions such as trigeminal neuropathic pain, pudendal neuralgia, and SCI-related neuropathic pain. More studies will be required to examine the long-term safety and efficacy of MSC therapies and their respective clinical applications. Future research employing the latest technical advances and experimental protocols hold the key to increasing scientific evidence required to effectively translate MSC therapies to clinical practice in pain management.

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