Chapter 8
Application of Stem Cells in Treatment of Bone Diseases: Pre-clinical and Clinical Perspectives

Mir Sadat-Ali

Abstract The word "Stem Cell" first appeared in the scientific literature in 1868. Stem cells are cells which have the ability to self-renew and give rise to differentiated cells. In 1960, McCullough and till reported that the living tissues came from stem cells and with the concept of self-renewal. In the twentieth century with the discovery of hESC, it was believed that stem cells will give potential therapies for the chronic human diseases. There was a flood of research in every field including orthopaedic surgery. As the Mesenchymal stem cells are able to develop into tissues including bone, cartilage, muscle, tendon, and ligament. Trials were instituted to treat non-unions, long-bone defects, spinal cord Injury, osteonecrosis of head of femur, spinal cord injury, osteochondral defects, osteoarthritis, rotator cuff injuries, and tendon and ligament ruptures. Stem cell therapy requires a clear comprehension of the orthopaedic disease process before clinicians embark on the new strategies to treat old diseases. It is also imperative that practicing clinicians to have a knowledge of different cell sources like autologous, allogeneic and iPSC, and the culture methods and their limitations.

It is also strongly recommended that orthopaedic surgeons should not give up the well-known recommended treatment modalities of treatment until stem cell therapy is proved safe, efficacious, and cost effective.

Keywords Orthopaedic surgery · Autologous · Allogeneic · Stem cells · Mesenchymal stem cells · Osteoblasts · Chondrocytes · Neurocytes

Introduction

In the last 2 decades, there has been enormous interests to treat chronic diseases through cellular therapy and tissue engineering. Two aspects were considered important visa vi the limit the cost of the care of the skeletal system in the aging population

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of the world and secondly to improve the quality of life. The process in the development took place in stages from 1800's to remove the diseased organs to 1960's replace the affected joints and ligaments, in 1980's the era of repair of the skeletal system, and from 2000's clinicians and researchers took the pathway to regenerate tissues. It was expected that by 2020, reproduction of the organs will take place which has not crossed the line of bench to the bedside. There are few specializations which are rapidly advancing in the field to utilize cellular therapy and orthopaedic and trauma surgery stands clearly ahead. This chapter will deal with the common chronic conditions of the musculoskeletal system highlighting the animal works to the transfer of technology to treatment human patients.

Short History of Stem Cell Development

Even though it was 1957, the first bone marrow transplant was performed to protect patients from after effects of radiation and chemotherapy (Thomas et al., 1957), but it was Friedenstein and associates (Friedenstein et al., 1966) and Tavassoli and Crosby (1968), who reported the osteogenic material in the bone marrow. The studies of Owen and Macpherson taught us. That osteoblasts precursors lined the inner layer of the periosteum (Owen, 1970; Owen & Macpherson, 1963). Recognizing and accepting the bone was a living organ, and it was shown that the role of bone marrow in the maintenance of hematopoiesis and hematopoietic stem cells (Dexter et al., 1973) showing that bone apart from being part of skeletal system giving attachment to muscles and ligaments for the body to move and protect and support vital organs had a major function of providing hematopoiesis and hematopoietic stem cells.

Caplan (1991) renamed the bone marrow Stroma as the bone marrow cells of the yester years to Mesenchymal stem cells which was well accepted by the scientific fraternity. It was brought to light that the MSCs had the potential to form osteoblasts the bone forming cells, chondrocytes, and adipocytes (Dominici et al., 2006). The reported work of Thomson and his colleagues in 1998 (Thomson et al., 1998) of achieving the isolation of human embryonic stem cells (hESC) pushed the research to treat diseases in a high gear, and many clinicians and general public believed that the treatment of many chronic untreatable diseases is around the corner. But the issues of the human embryos to provide the cells was still under cloud due to the ethical issues associated with hESCs when the major breakthrough came with the success of work of Takahashi and Yamanaka (2006) in creating induced pluripotent cells (iPSC) that can be generated directly from a somatic cells with the fast development in the field of stem cell and its potential use in chronic diseases has met with assumed cures and misuse of stem cell which failed to withstand serious scientific scrutiny.

Osteonecrosis of Head of Femur

Introduction

Avascular necrosis of the head of femur (ANFH) or osteonecrosis as it is termed is a common condition and type of osteonecrosis which occurs due to disruption of blood supply to the head of femur, and there are multiple causes which could be secondary to the trauma or diseases. In USA alone, yearly, there are 10,000–20,000 new cases are added with ANFH (Petek et al., 2019). Traumatic causes are due to the fracture neck of femur and hip dislocations, whereas diseases form the main bulk of ANFH. The common conditions which can be listed are chronic steroid use, alcohol consumption, and other risk factors include radiation therapy, chemotherapy HIV infection, Caisson disease, Gaucher's disease and in sickle cell hemeglobinopathy, and last but not the least idiopathic. Recovery of the ANFH without treatment does not occur and many patients go through with total hip arthroplasty (THA) for the relief of pain. Even though ANFH was first described in 1785, still we do not have a definite treatment for complete recovery of the head of femur (Tetik et al., 2011). Many methods have been tried to maintain the femoral head so that the final surgery of total hip arthroplasty can be avoided. Some of the procedures include bone grafting (Mont et al., 2007; Seyler et al., 2008), core decompression (Ficat et al., 1971; Lieberman, 2004; Lieberman et al., 2004; Mont et al., 2004), and electrical stimulation (Steinberg et al., 1989; Trancik et al., 1990). Extracorporeal shock wave therapy (ESWT) had initial success which reduced osteoblast apoptosis (Wang et al., 2005). But the results of these procedure were inconsistent. Long-term results of hip arthroplasty in young patients are below the norms due to the durability of implants. The results of the THR are usually unpredictable in this age group (Ince et al., 2006; Kim et al., 2011).

Pre-clinical Studies

In the recent past cell-based therapies, particularly mesenchymal stromal cells (MSC) for repair of damaged cartilage and relief of pain have been tried in experimental animals with excellent results. Abudusaimi et al. (2011) showed that direct transplantation of autologous adipose derived MSCs into an avascular area of the femoral head of the rabbit made new vessels to grow and new bone formation. Sun et al. (2011) reported that the results of forty rabbits which showed the core decompression stem cells injection in the avascular head of femur gave excellent results on histologic and histomorphometric analyses. They concluded that local transplantation of stem cells may prove an effective treatment option for steroid-induced osteonecrosis of the femur. The other reported animal studies had similar results (Aimaiti et al., 2011; Wen et al., 2012; Xie et al., 2012).

Clinical Studies

The concept of using stem cells via bone graft was attempted as early as 1987. Hernigou et al. (1997) treated a patient with SCD in with bone marrow concentrate in the affected area of the head of humerus and obtained with good results. Other researchers used bone marrow concentrate (BMC), bone marrow stromal cells (BMSCs), and MSCs were used (Lee et al., 2003; Li et al., 2011; Sen et al., 2012; Yoshioka et al., 2011). Hernigou and Beaujean (2002) used standard core decompression and BMC which produced excellent results at 60 months follow up and only 6.2% hips requiring total hip arthroplasty (THA). In 2012, Zhao et al. (2012) conducted a randomized control trail involving one hundred patients with early stage ANFH were recruited and randomly assigned to bone marrow derived mesenchymal stromal cells (BMMSC) treatment or core decompression (CD) treatment. At 5 years after the initial surgery, only 4% bone marrow derived MSC-treated hips progressed requiring further treatment. In CD group, 23% hips progressed and underwent further definite surgery. There were no complications in either groups. This intervention is safe and effective in preventing femoral head collapse, which require THA. In an extensive review on the subject Houdek et al. (2014) suggested that, CD combined with MSCs can provide significant pain relief, improvement in function, and ultimately halt the progression of AVN of the femoral head. Using this procedure, patients in young age can return to normal activities of daily living and avoid early hip arthroplasty. Piuzzi et al. (Persiani, 2015) performed an a systematic review with a level-of- evidence of III or higher evidence and reported that the avascular lesions in 24.5% after cellular therapy progressed compared with 40% in the controls. Ninety percent of studies that reported failure rates showed a lower THA conversion rate in the cell therapy group sixteen percent compared with the control group 21%. Sadat-Ali et al. (2017) reported in a small study in which they used osteoblasts injection derived from MSCs and found to me more effective as it healed all their patients who had grade 11 and III Ficat ANFH. In an extended study, the analysis of the 63 patients who had 5 million of osteoblasts injected at the site of the avascular lesion in patients <30 years with majority of female patients with of 49.05 $\pm$ 12.9 (range 24–60) months. The VAS and modified Harris hip score improved significantly ($p < 0.0001$). The Azam-Sadat score (ASS) for quality of life score for chronic diseases also significantly improved from 2.76 $\pm$ 0.49 preoperatively to 7.92 $\pm$ 0.09 ($p < 0.0001$) at 24 months. Overall 93.6% were satisfied with improved quality of life and only 4 (6.4%) the disease progressed and had to have total hip arthroplasty.

Conclusion

Reports of pre-clinical trials are few, and majority of the published data has concentrated on the clinical trials, and the literature gives a clear and more persuasive evidence to use cellular therapy in the ANFH. The type of cells used were the MSCs

and osteoblast injection in the healing of the avascular lesions and postponement of the THA. Since randomized and comparative studies are available for review, it is safe to say that cellular therapy is the treatment of choice in young patients with ANFH so that they live a more normal life.

Stem Cell Therapy in Fracture Healing

Introduction

Fracture healing is a very complex process which involves local and general factors. The reported incidence of impaired healing leading to non-union is 5–10% (Mills et al., 2017; Zimmermann & Moghaddam, 2010). The cost treating a non-union ranges in different countries differently. In USA, the hospital costs for each non-union is $25,556, and in Great Britain, it costs £16,330 GBP (Antonova et al., 2013; Kanakaris & Giannoudis, 2007). Delayed healing is usually due to failure of the local cellular structures to react to the stimulation of the growth factors which are released at the site of the fractures. In the last 40 years, surgeons got a boost to heal fractures way of rigid internal fixation (Allen et al., 1968; Allgower & Speigel, 1979), but only realized later that with adequate fixations fractures also failed to unite. The second method developed to heal fractures was mechanical stimulation (Claes et al., 1998; Hadjiargyrou et al., 1998; Ryaby, 1998). In such cases, there is a growing need to find ways to regenerate the fracture site so that adequate healing occurs in time and MSCs has been suggested a promising option. MSCs are part of the bone marrow cells which are present in the cavity of the bone and are known to give rise to cells like osteoblasts, chondrocytes, and endothelial cells which take active part in bone deposition (Bruder et al., 1994; Granero-Molto et al., 2009; Muguruma et al., 2006).

Pre-clinical Studies

In the pre-clinical field, initial studies in smaller animals like rats were quite successful. It was demonstrated as early as 2009 that MSCs can induce a fracture healing in animals with increase in the callus formation and contributed in the enhancement of all the stages of fracture healing (Undale et al., 2011). Bruder et al. (1994) have shown that the healing of the fracture depends on the quantity of cells is also an important factor, hence, injecting large number of MSCs become imperative in the healing process. Undale et al. (2011) used human MSCs to heal ununited fractures in rats. Their results indicated that both type of cells one hESC-derived MSCs and hBM-MSCs, healed the fractures good and in better time. Other studies as well reported similar results (Connolly et al., 1991; Goel et al., 2005).

Sadat-Ali et al. (Kassem, 2013) used osteogeneic differentiated cells from the MSCs instead of eESC or MSCs and used in experimentally created non-union in rats and achieved better results.

Clinical Studies

The early studies of use of MSCs in the non-union of fractures came from utilizing bone marrow injections. Connolly et al. (1991) injected autologous marrow in patients non-union of tibial fractures and achieved union in 80% of patients. This study paved the way to use bone marrow injection without much realization that MSCs were being injected to heal the fractures. Many studies reported similar results of success in healing of the non-unions using bone marrow aspirate injections (Guimarães et al., 2014; Sugaya et al., 2014).

Bajada et al. (2007) treated patient with a recalcitrant a nine year tibial non-union using autologous MSCs with calcium sulfate pellets which healed the fracture, and Kim et al. (2009) performed a multicenter, randomized clinical study of two groups of patients with non-union of the fractures; one control and had osteoblast injections. Patients with osteoblasts injection united with good results.

Recently Senthilkumar et al. (2018) compared three groups of patients one with MSCs and bone marrow aspirate and a control group. In the MSCs group 92.3% of fractures united, in the bone marrow aspirate group 40% of fractures united indicating the MSCs are more potent in uniting the non-unions. In a recent meta-analysis on human studies, Palombella et al. (2019) reported the data on 347 patients who were treated with different modalities of the stem cells and found that within a year of follow up 81–100% union took place. They concluded that bone marrow concentrate and bone marrow derived mesenchymal stromal cells (BMSCs) with scaffolds could be considered as treatment choice to treat non-unions.

Conclusion

Reports of clinical trials which are available in the literature does not give a clear and more convincing guide to use the cellular therapy in the non-unions as the reported studies used different cells with and without scaffolds. We need more structured and prospective randomized studies to recommend routine use. In the absence of other definite and successful treatments, the use of stem cells have demonstrated potential in the healing of fractures and non-unions where natural healing mechanisms are inadequate, and large number of Stem cells are needed for the fracture unions. Autologous stem cells in the form of MSCs and osteoblasts does play a role in providing a safe, non-immunogenic cells which can heal the non-unions.

Stem Cell Therapy in Osteoarthritis of Knee

Introduction

Osteoarthritis of Knee (OAK) is mostly due to aging process and was suggested many factors influence the severity of the disease. It has been extrapolated that in 2020, globally incidence of OAK annually is 86.7 million individuals >20 years and older (Jordan & Croft, 2005). In 2013, it was assessed that medical costs for treating osteoarthritis in USA was $140 billion (Cui et al., 2020) in direct costs and each year 6000 die in USA each year are due to NSAID-related complications and costing additional $2 billion (Ledingham & Snowden, 2017; Jawad & Irving, 2007; Brabant & Stichtenoth, 2005). The management of the OAK has been by non-steroidal anti-inflammatory drugs (NSAIDs), physical therapy, and nutritional supplements (Bellamy et al., 2006; Bruyere & Reginster, 2007; Clouet et al., 2009; Peat et al., 2001; Quinn et al., 2018; Schuh et al., 2007). Even though the prevalence has increased but the no new treatments have been added with all the treatments, available OAK progresses slowly till the joint is destroyed, and quality life is severely affected. On the other side, there are some patients who show rapid deterioration even after adequate treatment and end up having joint replacement. In OA, the knee is the joint most commonly affected (Chevalier, 2010). Some patients only require non-steroidal anti-inflammatory drugs (NSAIDs) and physical therapy and certain group of patients the disease progresses leading to severe disability. Many patients do not respond to the conservative therapies and require steroid and hyaluronic acid injections, arthroscopic joint washout with varying degrees of pain relief (Brittberg et al., 1996; Caminal et al., 2014; Moseley, 2009).

Pre-clinical Studies

In the recent past cell-based therapies, particularly mesenchymal stromal cells (MSC) for repair of damaged cartilage and relief of pain have been tried in experimental animals with excellent results. Cells (MSC) for repair of damaged cartilage and relief of pain in rabbits and sheep (Chiang, 2005; Grigolo et al., 2009; Im et al., 2001; Rahfoth et al., 1998; Shah et al., 2018). MSCs transplantation was shown to grow cartilage similar to hyaline cartilage and a high type II collagen presence. The efficacy of mesenchymal in a porcine model showed regeneration of hyaline cartilage in 180 days (El-Tookhy et al., 2008). Shah et al. (2018) studied over 200 dogs diagnosed with degenerative arthritis with severe chronic pain and limited activity. Allogenic adipose derived MSCs were harvested and given either intra-articular or intravenous. In this report, over 85% of dogs improved significantly in the physical activity. The study in healthy dogs, OA was created by partial-thickness cartilage defect. The effect of intra-articular injection of autologous derived chondrocytes was compared with allogenic derived chondrocytes indicated that recovery of the

damaged cartilage regenerated when compared with control groups (Goshima et al., 1991; Miki et al., 2015; Wakitani et al., 1994; Zhang et al., 2018).

Clinical Studies

Osteoarthritis of the knee (OAK) a very common degenerative disease for which there is no definite treatment for cure as the articular cartilage which is damaged could repair itself. In an aging knee, the chondrocytes behave in a different way; hence, complete repair does not take place. It was reported that MSCs from the bone marrow could replace the cartilage and bone, and this lead to the pre-clinical and clinical studies to treat OAK.[27–29] Wakitani et al. (2002) treated 24 patients with OAK used bone marrow aspirate and injected MSCs in the affected knees. They performed clinical and arthroscopy assessments. Their final conclusion was that autologous bone marrow derived MSCs have the ability to the repair osteoarthritic cartilage defects due to OAK in humans. Recently Jo et al. (2014) conducted a phase I/II A proof-of-concept clinical trial injected MSCs into the osteoarthritic knee. Post-injection analysis at 3, 6, and 12 months showed total relief of pain and better function of the knee joint with no adverse events. Soler et al. (2016) used autologous MSCs in patients with Grade II and III of Kellegren and Lawrence grading and found that an injection single intra-articular injection of the MSCs was safe and complete pain relief, improved quality of life up to 4 years and radiological signs of cartilage repair. A recent meta-analysis drew positive conclusions that MSCs could be treatment of choice to increase the function, reduce pain in knee OA. The findings of this review should be confirmed using methodologically rigorous and adequately powered clinical trials (Soler et al., 2016). Park et al. (2017) used allogenic hUCB-MSCs in patients with OAK and had a follow up for 7 years and concluded that even allogenic MSCs are safe to regenerate effected knees due to osteoarthritis. For long-term effective results, Invossa-K used allogenic chondrocytes with TGF-ß1 has been used with results by which TKR can be postponed for 5–7 years (Cho et al., 2017; Park et al., 2017). Lim et al. (2017) reported the use of "Cartistem" an allogeneic human umbilical cord blood-derived mesenchymal stem cells approved by the Korean FDA (KFDA) which also received US FDA clearance to conduct Phase III clinical trials in the USA. The Phase I and II trials reported safety and efficacy in the treatment of OAK. The final results of the follow up for 60 months are awaited. (NCT01041001).

Conclusion

Many different cellular therapies have been tried and reported, MSCs, chondrocytes, from Bone marrow, adipose tissue, autologous, allogeneic, umbilical cord blood, and different cell strength 2×10^6–5×10^7 cells per patient. Despite excellent work and results of articular cartilage regeneration under the influence of chondrocytes,

there are very few FDA-approved which are undergoing extended clinical trials. The literature is full of published data which gives from excellent to very good results which convince us that cellular therapy have an important role to play in the reversal of degenerative cartilage I which should pave the way for routine treatment option in OAK.

Stem Cell Therapy in Meniscus Injuries and Ligament Injuries

Introduction

Meniscus and ligament injuries are common in the young mainly due to sports-related activities, and it was found that per year the cost range between $446 million to $1.5 billion and reaches $19.2 billion yearly (Lim et al., 2017). Ligaments and meniscus have limited ability to naturally heal, and it is this reason these injuries have poor functional outcome. Many therapies have been in trials conducted and tried to repair and enhance the healing. The treatment of such injuries is always surgical if the meniscus is removed completely as it used to happen before can accelerate joint degradation and cause secondary osteoarthritis of knee. The use of stem cell in other conditions has encouraged clinicians to use stem cells, to intensify healing close to normal of the injured meniscus and ligaments.

Pre-clinical Studies

Initially, animal studies were carried out for meniscus injuries in rats and rabbits using stem cell derived from synovial membrane proved to be detrimental in healing of the iatrogenic meniscus defects created (Hatsushika et al., 2013; Horie et al., 2009). Ruiz-Ibán et al. (2011) studied the effect of adipose derived MSCs on avascular area of the meniscus and concluded that adipose derived MSCs healed the smaller and larger lesions which were created. In another comparative study, iatrogenic tears were created microminipigs in the medial meniscus of both knees and sutured. In one knee, MSCs were injected and the other was kept as a control. The healing was evaluated for 3 months, and the results showed that the MSC's group had a significantly better healing in all the parameters examined in the injected group (Nakagawa et al., 2005) Hatsushika and his colleagues (2014) reported that in their study, they treated large defects in the porcine model, but the meniscus healed under the influence of multiple injections of the MSCs, but could not ascertained how many injections was needed. Ferris et al. (2014) studied horses with autologous bone marrow derived MSCs by intrarticular injection and assessed arthroscopically and reported that the recovery of the meniscus healing appeared in 75% of the animals. Kanaya et al. (2007) studied

partial torn anterior cruciate ligament (ACL) injuries in Sprague-Dawley rats with intra-articular injection of bone marrow derived MSCs and found better healing of the ACL as compated to the control groups of rats. Similar outcomes were reported by Oe et al. (2011) used MSCs and found very similar results of excellent healing of the ACL repair under the cellular therapy. At 4 weeks, the assessment of stress tests and histological studies indicated normal findings as compared to the control group of animals.

Clinical Studies

Various clinical studies have shown that cellular therapy in the treatment of meniscus injuries shows promising results. Centeno and colleagues (2008) were the first report, where autologous mesenchymal stem cells was used to heal a torn meniscus. The result was astounding reduction of the pain, increased joint range of movements, and with healing of the meniscus. Al-Sayed et al. (2018) 16 patients with the mean of 34.8 ± 5.1 years with complete tears. The study reported that there was total reversal of pain, range of movement, and healing of the meniscus under the influence of chondrocytes.

Vangsness et al. (2014) performed a randomized study to study the effects of MSC injections into the knee after the medial meniscus was removed. A MRI done after a year showed significantly increase in the volume of the meniscus as compare to the control group. Recently couple of studies is smaller groups of patients confirmed the use of MSCs, and chondrocytes are effective in the treatment of meniscus repair. Onoi et al. (2019) arthroscopically looked pre- and post-injection of stem cells reported after six months showed improved meniscus status of repair. Sekiya et al. (2019) went one step further in confirmation of the efficacy of the stem cells in healing of the meniscus. Patients were followed up for 2 years clinically and a 3D MRI showed complete healing of the torn meniscus.

Conclusion

Reports in the English language literature of the pre-clinical studies demonstrated robustly the efficacy of the cellular therapy in the healing of meniscus and ACL. The same results were replicated in the clinical studies. Since there are different types of cells available, it is difficult to decide what to use and how much cells are to be given and how many times. One fact is proved that the autologous cellular therapy is safe and effective. More randomized control trials are needed, and based on the results of such studies, the repair of meniscus using cellular therapy can be labeled as standard of care.

Stem Cell Therapy in Management of Osteoporosis

Introduction

Osteoporosis is an ageing disease which is common all over the world and is a serious health issue as 200 million people suffer worldwide (Vijayakumar & Büsselberg, 2016). The end result of osteoporosis is fragility fractures, which increase morbidity and mortality. As of 2005, it was reported there were >2 million fractures, costing $18 billion, and it is estimated that by 2025, annual fractures and costs will increase to $30 billion (Burge et al., 2007). Osteoporosis causes fractures with a mortality of 15–30%, which is quite similar to many chronic diseases (Cooper et al., 2011). The pharmacological therapy is based on either anti-resorptives or anabolic agents (Fukumoto & Matsumoto, 2017). There are only 4–5 drugs which physicians have to control the disease and prevent fractures. The most common adverse events, particularly for oral bisphosphonates, upper esophageal causing irritation and bleeding, atrial fibrillation and renal failure, and excretion of the drug happens through the kidney patients with kidney disease cannot be used. Atypical femur fractures and bisphosphonate-related osteonecrosis of the jaw are serious complications of bisphosphonate use (Garg & Kharb, 2013; Pazianas & Abrahamsen, 2016). The anabolic agent has its own complications of cost, restricted use, and duration of use. There is need of an agent which should be inexpensive, efficacious, and free from routine complications. Millions of patients will benefit from the stem cell applications and osteoporosis is one of them, and research should be more focused on diseases like osteoporosis.

Pre-clinical Studies

Osteoporosis is one of the ten targeted diseases to be studied using stem cell therapy, but studies were slow to start on this chronic disease (Perry, 2000). Wang et al. (2006) initially showed in osteoporotic rabbits that injections of bone marrow derived MSCs can increase bone formation in the study group in comparison to the control group of animals. Ocarinao and his group (Wang et al., 2006) studied the effect of bone marrow derived MSCs (BMMSCs) in bilaterally ovariectomy induced Wistar rats. They injected 0.75 million cells in the femur and histology and histophotometric analysis revealed improved bone strength. They concluded that osteoporosis could be treated BMMSCs. Using adipose derived stromal cell therapy in rats proved that the injections prevents bone loss in ovariectomized mice (Ocarino et al., 2010). Kiernan et al. (Cho et al., 2012) reported that their study showed that transplanted MSCs led to better bone formation mice with low bone mass after a single injection of MSCs. Sadat-Ali et al. (2018) used autologous bone marrow derived osteoblasts in ovarectemized rats who had developed osteoporosis. Rats were injected osteoblasts in the tail veins

and were euthanized at 8 weeks, and bone morphology was examined using high-resolution peripheral quantitative computerized tomography (HRpQCT). Results indicated that there are large quantity of the new bone in the study groups as compared to the control group of animals. Another study with direction of future research in osteoporosis compared three different cells MSCs, osteoblasts, and exosomes derived from osteoblasts in ovariectomy induced osteoporosis in rats. Results suggested that under the influence of osteoblasts, bone formation was significantly more than the other groups (Sadat-Ali et al., 2019).

Clinical Studies

Even though there is robust data available on animal studies, only two clinical trials have been instituted. The first study involving 8 patients used allogeneic mesenchymal cell from umbilical cord and assessment was made by visual analog scale, improvement in the range of motion, results of bone mass density, and improvement in patients quality of life (ClinicalTrials.gov Identifier: NCT01532076). The second ongoing trial is using autologous bone marrow derived MSCs in the range of 2–5 million cells/kg (ClinicalTrials.gov Identifier: NCT02566655).

Stem Cell Therapy in Spinal Cord Injury

Introduction

Spinal cord injury (SCI) is a major cause of paralysis in young, and the majority is due to motor vehicular accidents. Over two hundred and fifty thousand US citizens are suffering with spinal cord injury. Half of those injured become paraplegic and >40% quadriplegic. Over 80% of the injured are males, and 56% of injuries occur between the ages of 16 and 30 years (The University of Alabama National Spinal Cord Injury Statistical Center, 2002). The total direct costs for spinal cord injury are a staggering direct costs for all causes of SCI in the USA are $7.736 billion, solely for direct costs related to the injury (DeVivo, 1997). The estimated traumatic SCI occurs worldwide is annual incidence of 15–40 cases per million (Toma et al., 2005). Many preventive measures have been taken to reduce the SCI, but the incidence is increasing. To make matters difficult at present, we do not have effective therapies to reverse this disabling condition. Efforts to reverse this disabling injury have been tried with little or no success. There is plethora of studies which are ongoing in both the pre-clinical and clinical aspects and soon something positive is bound to happen.

Pre-clinical Studies

It was Koshizuka and colleagues (2004) first initiated the study on stem cells in spinal cord injured mice. They transplanted hematopoietic stem cell after a week of the injured cord. The assessment included the recovery of hind limb function, which showed a good recovery from 3 weeks of the cellular therapy. Histologically it showed that the injected HSCs from bone marrow differentiated into glial cells and neural precursors in the injured spinal cord. The mice were able to walk with partial weight on their hind legs, and in the control, mice could not walk nor could weight bear on the hind limbs. No weight bearing on their hind limbs. They concluded that the HSCs had the potential to help in the recovery of the injured spinal cord. Iwanami et al. (2005) studied primates with iatrogenic spinal cord injured and used the neural cells. After 2 months of transplantation, histologic analysis revealed that the grafted human NSPCs survived and differentiated into all the neural cells. Syková et al. (2006) injected mesenchymal stem cells (MSCs) in the treatment of spinal cord compression lesion in rats. The functional improvement was seen in MSC-treated rats. The conclusion of the study was that treatment with MSCs can improve had the behavioral outcome and histopathological assessment in rats. Following decade showed many such studies and very similar results showing the efficacy of the stem cells in the recovery of the injured spinal cord in animals (Hur et al., 2016; Kim et al., 2016; Morita et al., 2016; Watanabe et al., 2015; Yousefifard et al., 2016; Zhou et al., 2016). In another meta-analysis of 5628 animals with different experimental protocols indicate that with the use of allogeneic stem cells, the improvement after spinal cold injury is 25% (Antonic et al., 2013). Sadat-Ali et al. (2020) compared autologous bone marrow derived neurocytes versus rESC. The animals were assessed using Basso, Beattie, Brenham scoring, electromyographic studies, and histopathological analysis. The results indicated significant improvement in rats receiving rESC and autologous bone marrow derived neurocytes as compared to the control group. Comparison between autologous bone marrow derived neurocytes and rESC groups, the recovery in autologous bone marrow derived neurocytes was much better than rESC.

Clinical Studies

Based on the robust animal studies, Jeon et al. (2010) performed a clinical trial to test the efficacy of autologous MSCs therapy for spinal cord injury in humans. They assessed the recovery using electromyography, evoked potential, and magnetic resonance imaging (MRI). In 60% of the patients, there was improvement of the motor power and sensory changes. In the last 10 years, over 200 patients with acute and chronic spinal cord injured. Most of the patients received autologous MSCs, but the route of administration was from intra-thecal, epidural space, intra-lesional, and intravenous. Secondly, the quantity of the cells is ranged from 8 to 10 million MSCs.

Majority of patients improved in the functions in varying percentages, and there was no adverse reaction reported in these patients due to treatment. At present, over 10 clinical trials are ongoing in various countries in Phase I/II and III.

Conclusion

Stem cell therapy is an important modality which needs expeditious research to formulate a treatment protocol to treat spinal cord injured patients who remain paralyzed with low quality of life. The pre-clinical trials have shown great promise, but this could not yet be translated in the clinical trials. Clinical trials have shown moderate recovery and partial improvements in the life style of patients. Clinicians and researchers need to come together with clear strategy and conduct clinical trials without bias to achieve expectations of the patients. Clinical trials in healing of the injured spinal cord need to be more organized with clear cut protocols in type of cells, dosage of number of cells, route of administration, and how soon after the injury cellular therapy should be instituted.

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