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Challenges of stem cell therapies in companion animal practice



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ABSTRACT

Regenerative medicine using stem cells from various sources are emerging treatment modality in several refractory diseases in veterinary medicine. It is well-known that stem cells can differentiate into specific cell types, self-renew, and regenerate. In addition, the unique immunomodulatory effects of stem cells have made stem cell transplantation a promising option for treating a wide range of disease and injuries. Recently, the medical demands for companion animals have been rapidly increasing, and certain disease conditions require alternative treatment options. In this review, we focused on stem cell application research in companion animals including experimental models, case reports and clinical trials in dogs and cats. The clinical studies and therapeutic protocols were categorized, evaluated and summarized according to the organ systems involved. The results indicate that evidence for the effectiveness of cell-based treatment in specific diseases or organ systems is not yet conclusive. Nonetheless, stem cell therapy may be a realistic treatment option in the near future, therefore, considerable efforts are needed to find optimized cell sources, cell numbers and delivery methods in order to standardize treatment methods and evaluation processes.

Keywords: Canine; clinical trials as topic; feline; regenerative medicines; stem cells

INTRODUCTION

Recently, the demand for cell-based therapies for various refractory diseases has been increasing. Stem cells have a wide, sometimes unlimited, differentiation potential in various body organs, and possess the capacity for self-renewal. This makes stem cell transplantation an attractive therapeutic candidate for patients with a wide range of incurable diseases and injuries [1-4]. According to recent human studies, the number and type of stem cells in clinical trials have expanded [5-9].

Among the various stem cells, mesenchymal stem cells (MSCs) are the most favored and routinely exploited cell type in the clinical trials [1,10]. Basically, they can be easily collected and isolated from bone marrow (bone-marrow-derived MSCs; BMSCs) and adipose tissue (adipose tissue-derived MSCs; AD-MSCs). MSCs have the capability to differentiate into chondrocytes, adipocytes, osteoblasts, myocytes, neural cells and hepatocytes [11-15].

Author Contributions

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Although MSCs from various sources share many biological features and characteristics, differences have been reported in their immunophenotype, proliferative capacity, differentiation potential, immune modulation and gene expression profiles [1,16,17]. Consequently, the application and effectiveness of each type in veterinary clinical practice may differ [18,19].

Even though stem cell treatment has potential benefits, the true therapeutic efficacy and adverse effects of stem cell therapy are not fully understood [12,13,20]. Several studies have suggested the possibility of adverse reactions during intravenous stem cell transplantation [13,20,21]. Additionally, many veterinary stem-cell treatments studies contain design flaws that limit the reliability of the results. For example, some failed to maintain consistent therapeutic protocols and lacked control groups or blinded evaluation [22-26].

Most recent stem cell reviews in veterinary medicine describe animal models for stem cell research for human disease. These studies mainly focused on various stem cell types and their potencies [27-29]. Expanded cell types and treatment protocols have been tested in canine models for clinical application in both humans and animals. Only one literature review describes the clinical use of AD-MSCs for spontaneous animal disease [19]. Before stem cells can be used in companion animal treatment, their safety and efficacy should be proven. The present literature review focuses on the clinical application of cell-based treatment for spontaneous diseases of different organ system in dogs and cats. To determine the status, challenges, and future prospects of stem cell therapy in veterinary medicine, we analyzed some of the most relevant clinical studies, and investigated treatment and evaluation methods.

BASICS OF STEM CELL TRIALS

It is well known that stem cells are unspecialized cells with the ability to self-renewal and differentiation of specialized cell types [1,28]. Regenerative medicine using stem cells was first used to treat hematologic diseases via bone marrow transplantation in late 1900s [30]. By 2000, the utility of stem cells had expanded to include non-hematologic disease such as cardiologic and neurologic diseases [5,10,31-33]. Stem cells can be classified under 2 large categories based on their sources: embryonic stem cells (ESCs) and adult stem cells (ASCs) [34]. ESCs have more developmental possibility than ASCs, but these stem cells have ethical and legal issues and safety concerns, including tumorigenicity [35]. ASCs can derived from bone marrow, peripheral blood, umbilical cord blood and tissue, adipose tissue, skin, neuron and muscle [1]. Recently, it has been discovered that pluripotent stem cells can be generated directly from adult somatic cells via genetic reprogramming. There are known as induced pluripotent stem cells (iPSCs) [36].

Stem cell treatment involves using stem cells to treat various disease or conditions. Stem cells are collected, transformed into specific types of cells via cell culture, and transplanted into the body. The stem cells and their derivatives then replace and heal damaged tissues. The curative effects of stem cell treatment can be evaluated differently depending on the primary disease, though it is typically accomplished by testing the structural and functional restoration of the target organ (**Fig. 1**) [34].

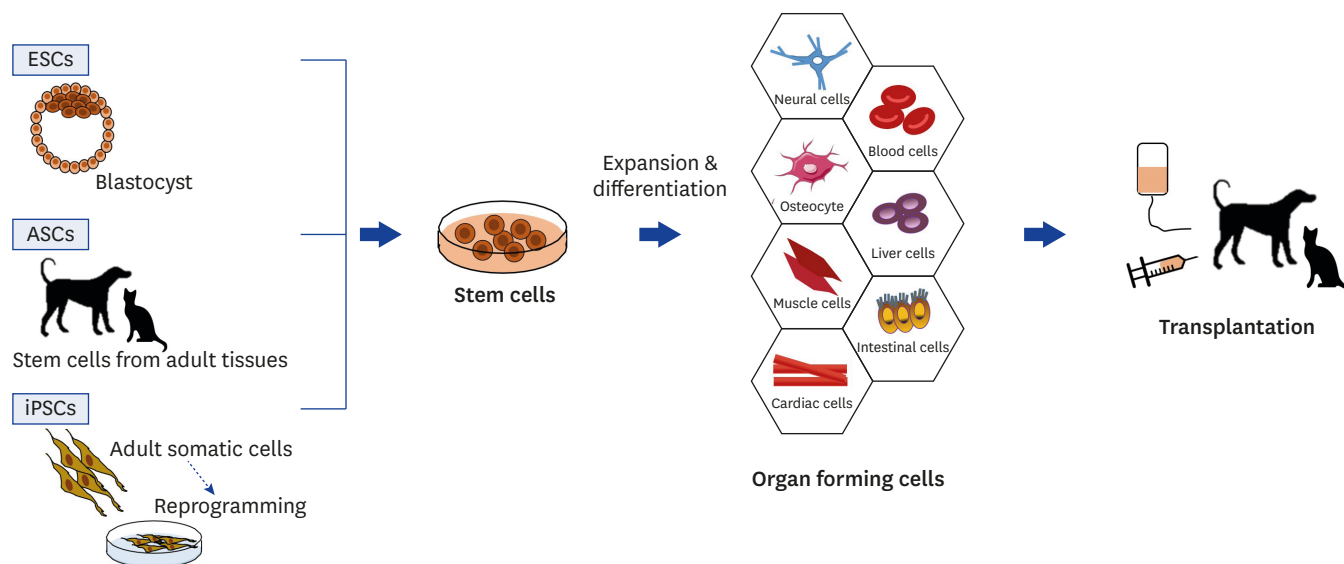


Fig. 1. Schemes of basic concept and procedures for stem cell transplantation. Stem cells can be classified into ESCs, ASCs and iPSCs based on their sources. Simply, stem cells are expanded to specific types of cells and transplanted into the body. ESC, embryonic stem cell; ASC, adult stem cell; iPSC, induced pluripotent stem cell.

STEM CELL TRIALS IN CARDIOVASCULAR DISEASE

Interestingly, stem cell therapy is an emerging potential therapeutic modality for cardiovascular disease [31]. Stem cells are commonly applied in myocardial infarction cases, because treatment is difficult and damaged cardiomyocytes are rarely regenerated [10]. Treatment protocols vary depending on the transplanted cell type, delivery method, time of administration and frequency [33].

Various types of stem cells have been used for cardiac therapy, including skeletal myoblasts, BMSCs, ESCs, endogenous cardiac stem cells (CSCs), AD-MSCs and even iPSCs generated from human hair follicle keratinocytes [37-39]. Among these, BMSCs have 2 advantages: lower immunogenicity compared to the other types of stem cells, and the action of paracrine growth factors [39]. It is demonstrated that preclinical studies have shown the ability of MSCs to attenuate cardiac remodeling, restore cardiac function, and regenerate damaged myocytes in acute and chronic canine models [40,41]. iPSCs generated from human hair follicle keratinocytes can differentiate into a cardiogenic lineage and function as a biological pacemaker, allowing for their potential application as a novel therapy for the advanced treatment of atrioventricular block [37]. Theoretically, autologous transplantation of CSCs is also possible. A previous study has demonstrated that attenuation of left ventricle remodeling causes less fibrosis in canine model of myocardial infarction after autologous CSCs intramyocardial injection [33].

The stem cell transplantation method is also important for enhancing therapeutic efficacy and safety. Previously, stem cells were introduced into cardiomyocytes by either direct intramyocardial (subendocardial or subepicardial) injection or intracoronary injection [42,43]. Direct intramyocardial injection has the advantages of providing precise targeting of cell delivery to the ischemic region and higher cell retention compared with intracoronary injection. However, direct injection may induce subsequent inflammation, which reduces the survival of engrafted cells [43,44]. Intracoronary injection presents a high risk of coronary

embolism and low stem cell retention. To overcome these disadvantages, other stem cell delivery methods have been developed and utilized. Ultrasound-mediated microbubble destruction induced by micropump in intracoronary injection increases the vascular permeability, which enhances the homing of BMSCs into cardiomyocytes and increases cardiac function [44]. Another study introduced percutaneous retrograde coronary injection in combination with basic fibroblast growth factor (bFGF) [43]. Combination with bFGF enhances the efficacy of BMSCs by increasing the migration and viability of MSCs and promoting their differentiation into the cardiomyocyte phenotype.

Only 2 studies have described cell-based treatment in veterinary clinical cardiac disease (**Table 1**). One study used allogeneic cardiosphere-derived cells in 5 dilated cardiomyopathy (DCM) dogs [45]. The beneficial effects of stem cell application were not detected in dogs with DCM during a 1-year follow-up. Another study transplanted allogeneic puppy deciduous teeth stem cells for the treatment of degenerative valvular heart disease [46]. The efficacy of treatment was evaluated for 2 months and resulted in improved heart function with alleviated clinical signs of heart failure.

Because myocardial infarction is rare in dogs and cats [47], all of these implications of stem cell therapy for the resolution of cardiomyocyte damage are limited by the experiments due to the use of small and no-randomized samples. Although few pilot studies provide alternative treatment options for cardiovascular disease in veterinary clinics, further research and clinical trials are needed to evaluate the short- and long-term efficacy and complications of stem-cell treatment.

STEM CELL TRIALS IN NEUROLOGIC DISEASE

Spinal cord injury (SCI) causes temporary or permanent neurological defect in humans and companion animals [32]. Because SCI is a devastating condition in humans, several therapeutic experiments using canine SCI models and clinical trials with natural spinal cord-injured dogs have been conducted as preclinical trials [27,32]. Most of the injuries were induced by balloon catheter compression methods between T13 and L3 [48-55]. Few studies have used unilateral spinal cord hemisection between T11 and L2 [56,57]. Stem cells from either canine or human origin were used, most being allogeneic canine MSCs [51-55]. The transplantation time and dose after injury varied, and a small number of dogs (under 10 dogs in each group) were treated. Although these limitations make the efficacy of stem cell therapy inconclusive, several studies have shown promising improvements in functional outcomes and have proven a greater clinical benefit for stem cell therapy in comparison with the traditional treatment.

Table 1. Veterinary clinical stem cell trials in cardiovascular disease

Disease	Cell therapy	No. of dogs	Control	Evaluation periods/effects	Ref.
Dilated cardiomyopathy	Allogeneic cardiosphere-derived cells; intra-coronary artery (20 × 10 ⁶ cells at left main artery and 10 × 10 ⁶ cells at right coronary artery)	5 dogs in stem cell group	Yes	At day 1, 1, 2, 6, 12 months; No adverse events and no significant effects occurred during and after cell infusion.	[45]
Degenerative valvular heart disease	Allogeneic puppy deciduous teeth stem cells; intravenous; 1 × 10 ⁶ cells 2 times with 14-day interval	10 dogs in stem cell group (combination with stem cell therapy and standard treatment); 10 dogs in control group (only standard treatment)	Yes	At 30 and 60 days; left ventricular ejection fraction and quality of life scores were improved in study group.	[46]

Along with the experimental research, 9 studies evaluated the efficacy of the stem cell treatment in veterinary SCI clinical cases [58-66] (**Table 2**). Acute and chronic clinical spinal cord-injured dogs were treated with various stem cell protocols. Most of the trials used autologous BMSCs, one study used allogeneic AD-MSCs [63], and 2 other studies used olfactory mucosal or glial cells [60,61]. Seven studies concluded that stem cell transplantation was beneficial and improved locomotor function; however, most of the studies involved a small number of dogs, and only 3 studies include control groups. Two studies failed to show the distinct clinical beneficial effects of stem cell treatment [60,64]; however, they also concluded that stem cell treatment was safe, and there may be some beneficial effects of stem cell therapy in companion animals with SCI.

Table 2. Veterinary clinical stem cell trials in neurologic disease

Disease	Cell therapy	No. of dogs	Control	Evaluation periods/effects	Ref.
SCI (T3-L7)	Autologous NIBM-MSCs; intra spinal injection; 5.0×10^6 cells for 2 times with a 21-day interval.	13 dogs in stem cell group	No	At 2, 5, 7, and 12 months; improvement in gait score in 6 of the cases, and improvement in proprioception and nociception in 2 cases	[58]
SCI	Autologous NIBM-MSCs; intra spinal injection; 5.0×10^6 cells 2 times with a 21-day interval.	7 dogs in stem cell group	No	At 2, 4 and 8 months; some beneficial effect of intraspinal injection of autologous NIBM-MSCs in dogs with paraplegia	[59]
SCI (T10-L4)	Autologous olfactory mucosal cells; intraspinal transplant; 6.24×10^6 cells	23 in stem cell group; 11 in control group (received cell transport medium alone)	Yes	At 1, 3 and 6 months; no evidence for concomitant improvement in long tract function	[60]
Severe SCI (T11-L2)	Autologous olfactory glial cells; intraspinal transplant; 5×10^4 cells	8 dogs in stem cell group	No	From 2 months to 1 year; the transplantation procedure itself is non-injurious and feasible; beneficial effect on locomotion	[61]
SCI	Allogenic AD-MSCs; intra spinal injection; 1×10^7 cells	9 dogs in surgery and stem cell group; 25 dogs in surgery group	Yes	Follow-up more than 6 months; better recovery outcomes compared to decompression surgery alone	[62]
Severe acute SCI (T6-L5)	Autologous BM stromal cells; IT into the CSF; 1.0×10^6 cells to 6×10^6 cells (mean, 3×10^6 cells) 3 times at 1-week intervals	7 dogs in stem cell group	No	Follow-up until 29-62 months after SCI; there were no complications; Only 2 of 7 dogs regained the ability to walk, no changes in sensory function	[63]
SCI (T13-L7)	Autologous BMSCs; intraspinal transplant (intraparenchymal); 1×10^6 cells in each 1 cm^3 of lesion	4 dogs in stem cell group	No	At 100 days, 12 months and 18 months; faster clinical recovery and improved movement in 3 of the 4 dogs; no changes in magnetic resonance imaging	[65]
Severe SCI (T11-L4)	Autologous BM-MNCs; subarachnodal to the lesioned spinal cord; 4.5×10^6 to 2.3×10^9 cells (mean, 8.88×10^7 cells)	36 dogs in stem cell group; 46 dogs in control group	Yes	Ambulatory recovery rate was assessed (mean time of ambulatory recovery was 34.84 days); significant increase in the recovery rate was revealed	[66]
Chronic SCI	Autologous BMSCs; IT into the cerebrospinal fluid; 0.3×10^5 cells to 3×10^6 cells (median, 1.3×10^6 cells) 3 times at 1-week intervals	10 dogs in stem cell group; 13 dogs in control group	Yes	At 1, 2, 3, 4, 5, and 6 months, until 6-35 months; there were no complications; improvement of pelvic limb locomotor function	[64]
Meningoencephalomyelitis of unknown origin	Autologous BMSCs; IT in the cisterna magna (2.0×10^6 cells), IV (0.5×10^6 cells), and IA in the right carotid artery (4.0×10^6 cells)	8 dogs in stem cell group (3 in IT + IA, 4 in IT + IV, 1 in IT + IA after IT + IV)	No	For 6 months up to 2-year follow-up; No major short- or long-term adverse effects; early improvement in general and neurological conditions, IT + IA group showed a shorter time of reaction to therapy	[78]
Fibrocartilaginous embolic myelopathy	hUCB-MSCs; percutaneous transplantation into parenchyma; 1.0×10^6 cells	1 dog	No	At 12 weeks; locomotor functions improved following transplantation.	[68]

SCI, spinal cord injury; NIBM-MSC, neurogenically-induced bone marrow-derived mesenchymal stem cell; IV, intravenous; IA, intra-arterial; IT, intrathecal; AD-MSC, adipose tissue-derived mesenchymal stem cell; BM, bone-marrow; BM-MNC, bone marrow-derived mononuclear cell; BMSC, bone-marrow-derived mesenchymal stem cell; hUCB-MSC, human umbilical cord derived mesenchymal stem cell.

Fibrocartilagenous embolism (FCE), which results from SCI, cause ischemic myelopathy in dogs [67]. One clinical trial utilized human umbilical cord (hUCB)-derived MSCs in an FCE-suspected dog [68]. hUCB-derived MSCs was transplanted 7 days after decompression surgery. As a result, locomotor functions improved following transplantation in this dog.

Along with SCI, stem cell treatment is applied in other neurological disease cases due to its immunomodulatory capacity and the neuroprotective and regenerative effects of paracrine factors induced by stem cells [69-71]. Canine meningoencephalomyelitis of unknown origin (MUO) is an intracranial non-infectious inflammatory disease [72,73]. The exact pathogenesis is still unclear, and immunosuppressive drugs are widely used as treatment options [72,74]. Similar to canine MUO, human multiple sclerosis, also known as chronic autoimmune inflammatory disease, is induced by the attack of autoreactive T-cells [75]. The immunomodulatory capacity of MSCs was tested in an experimental rodent model of autoimmune encephalomyelitis, and beneficial effects were seen as a result [76,77]. One study was conducted in which dogs affected by MUO were given MSC treatment [78]. Autologous BMSCs were administered by intrathecal injection in conjunction with intravenous and intra-arterial injection in the right carotid artery in 8 dogs. All dogs showed early improvement in their general and neurological conditions without complications. However, this study divided 8 dogs into 3 treatment groups with different stem cell administration protocols and had no control groups. Thus, the treatment effects of stem cells in canine MUO are still uncertain.

Promising improvements have been made in numerous studies using canine experimental SCI models, and these early results have led to clinical trials of stem cell therapy for various neurologic disease, including SCI cases. Further studies with controlled conditions are needed to verify the efficacy of stem cell therapy in companion animals with neurological disease.

STEM CELL TRIALS IN DERMATOLOGIC DISEASE

Normal skin is constantly being renewed and maintaining homeostasis using a pool of ASCs [79]. The basic process of skin wound-healing can be classified into inflammatory, proliferative, and maturation phases. The proliferation and remodeling phases require the complex processes of re-epithelialization, angiogenesis, stem cell activation, extracellular matrix remodeling, and scar formation [80]. As previously described [81-83], MSCs transplantation have demonstrated the therapeutic effects in skin wounds and dermal regeneration [81-83]. One study demonstrated the topical injection of BMSCs in an experimentally induced skin wound canine model [83]. The researchers concluded that BMSCs migrated to the region of inflammation, resulting in rapid re-epithelialization, angiogenesis, and increased collagen deposition. Two clinical cases demonstrated application of stem cells in large skin wound (**Table 3**). Autologous AD-MSCs with platelet-rich plasma was applied in a dog with the large skin defects due to train accident [84]. This case report showed complete closure of the wound 3 months after the stem cell transplantation. Another study showed 2 dogs with chronic chemical burn injuries that were not resolved with conventional treatments (16 and 24-month history) [85]. Both dogs were treated with regenerative therapy using human MSCs with poly (vinyl-alcohol) hydrogel membranes, and complete epithelialization was observed after 2 months. These 2 clinical cases only demonstrated individual cases without controls. However, considering the treatment results of these cases, it can be concluded with some certainty that regenerative therapy using stem cells improves the wound healing process. In addition to skin wound

Table 3. Veterinary clinical stem cell trials in dermatologic disease

Disease	Cell therapy	No. of dogs	Control	Evaluation periods/effects	Ref.
Skin wound (trauma)	Autologous adipose derived MSCs + platelet-rich plasma; spraying the cells over the wound surface (5 applications at day 11, 17, 23, 31, 41)	1 dog	No	A complete closure of the wound occurred 3 months after the start of the regenerative therapy	[84]
Chronic skin wound	Human MSCs + poly (vynil-alcohol) hydrogel membranes; locally infiltrated; 1×10^5 cells/cm ²	2 dogs	No	A complete epithelialisation was observed after 2 months	[85]
Hepatocutaneous syndrome	Allogenic adipose-derived MSCs; IV and intrahepatic injection; 5×10^7 cells for 46 times	1 dog	No	Follow-up for 32 months; stem cell therapy may extend a patient's survival time.	[86]
AD	Autologous adipose-derived MSCs; intravenous route; 1.3×10^6 cells/kg	5 dogs in stem cell group	No	At 2–3, 6–8, 10–12 weeks; the results were safe but not effective for controlling clinical signs and pruritus induced by AD.	[23]

AD, atopic dermatitis; MSC, mesenchymal stem cell; IV, intravenous.

repair, application of AD-MSCs in one dog with hepatocutaneous syndrome (HS) has been reported [86]. This dog showed a favorable response to stem cell treatment for a long time. HS induces superficial necrolytic dermatitis associated with liver disease [87], and MSCs were applied for dermal and hepatocyte regeneration [80,83,88].

MSCs exert their beneficial effects on the treatment of immune-mediated diseases by inhibiting the proliferation of T-cells, B-cells, and dendritic cells [76]. They also alter the maturation of antigen-presenting cells and the cytokine secretion [2]. Because of the immunomodulatory effects of the MSCs, clinical trials using MSCs in atopic dermatitis (AD) have been conducted in dogs [23]. In this study, autologous AD-MSCs were intravenously administered to 5 dogs with AD. No specific adverse effects were observed, but they failed to improve clinical signs.

Because of the repairing and regenerative capabilities of stem cells, most research has focused on clinical therapeutic applications of stem cells for damaged tissues and skin repair [3]. Recently, the application of stem cells has extended to incurable and recurrent immune-mediated skin diseases that have not responded to the conventional treatment. However, there is a lack of research on appropriate cell sources, mechanisms of action, efficacy, and safety of clinical trials in veterinary medicine.

STEM CELL TRIALS IN GASTROINTESTINAL (GI) DISEASE

The management of GI diseases is often challenging because of the complex pathogenesis, morphology and function of the GI system [89]. Various pathogeneses include infection, inflammation, neoplasm, and functional disturbance. Stem cell therapy may play an important role in human GI disease. Ongoing clinical trials with stem cells have been reported in disease that are difficult to treat, such as cirrhosis and liver failure, inflammatory bowel disease (IBD), and pancreatitis [89-91]. Many preclinical studies have shown promising results in human medicine, and these clinical approaches have also been tested in veterinary medicine.

The effects of autologous BMSCs and AD-MSCs were investigated in formocresol-induced oral ulcers in dogs [92,93]. Both studies demonstrated the rapid healing of induced oral ulcer following stem cell therapy compared with other treatments or control groups. This was most likely accomplished through angiogenesis and epithelial/connective tissue proliferation. The gene expression levels of angiogenesis and epithelial/connective tissue markers such as vascular

endothelial growth factor (VEGF) and collagen [93], VEGF, collagen, platelets-derived growth factor and epidermal growth factor [92] were significantly higher in the MSC-treated group.

IBD is a multifactorial, idiopathic infiltration of inflammatory cells in the small and large intestines. Lymphocytic-plasmacytic colitis is the most common form in dogs and has several histopathologic and molecular features that resemble human IBD [90,94]. The efficacy of a single intravenous injection of allogeneic AD-MSCs was evaluated in 11 dogs with IBD [95,96]. While the dogs were partially tolerant to conventional therapy, MSCs transplantation improved clinical scores, serum albumin, and serum biomarkers (folate and cobalamin) when compared to baseline [96]. Further evaluation with endoscopic and histological scales showed improved macroscopic changes (endoscopic index), but no improved microscopic histological scores [95]. Although the small sample size and absence of a control group or qualified evaluation methods may obscure the real effects of MSCs, these data provide a short-term safety and therapeutic potentials of allogeneic MSCs in dogs with IBD.

Canine anal furunculosis (CAF) is a chronic, immune-mediated disease in dogs characterized by the occurrence of perianal fistulas that resemble fistulizing Crohn's disease (one type of IBD) in humans [90,97]. Over 80% of CAF is diagnosed in middle-to-old-aged German shepherd dogs, but the pathogenesis of CAF, except for the genetic causes, is not fully understood [98,99]. Long-term immunosuppressive drugs are the most effective therapy, but relapses and refractory cases are common [97]. The efficacy of intralesional injection of human ESC (hESC)-derived MSCs in 6 dogs with refractory CAF was evaluated [100]. The hESC-MSCs were well-tolerated, and all 6 dogs were free of fistulas at 3 months post-injection. However, 2 of the 6 dogs experienced recurrence of fistulas by 6 months, indicating that multiple injection may be required in some cases.

There were only 3 feline stem cell studies in GI disease (**Table 4**). One feline study was conducted on chronic enteritis (lymphocytic-plasmacytic enteritis) [101]. Allogeneic feline AD-MSCs were administered, and clinical improvements were observed compared with the placebo at the 2-month follow-up. Two other studies administered systemic autologous or allogeneic feline AD-MSCs in refractory feline chronic gingivostomatitis (FCGS) [102,103].

Table 4. Veterinary clinical stem cell trials in gastrointestinal disease

Disease	Cell therapy	No. of dogs	Control	Evaluation periods/effects	Ref.
Inflammatory bowel disease	Allogeneic adipose-derived MSCs; IV; 2×10^7 cells/kg	11 dogs in stem cell group	No	At 6 weeks; the dogs were well tolerated and given clinical benefits. At pre-treatment and between 90 and 120 days post-treatment; endoscopic remission in 4 dogs and histological remission was not achieved	[95,96]
Anal furunculosis	hESC-derived MSCs; intra-lesional injection within the dermis and subcutaneous tissue around the perianal fistulas; 2×10^7 cells	6 dogs in stem cell group	No	At 7, 30, 60, 90, 180 days; the safety and therapeutic potential of hESC-MSCs were revealed.	[100]
FCGS	Allogeneic AD-fMSCs; IV; 20×10^6 cells, 2 times, 1 month apart	7 cats in stem cell group	No	At 1 month, 3 months, and 6 months; clinical improvement and resolution in 4/7 cats; cured ~12–20 months	[102]
FCGS	Autologous AD-fMSCs; IV; 20×10^6 cells, 2 times, 1 month apart	7 cats in stem cell group	No	At 1 month, 3 months, and 6 months; clinical improvement and resolution in 5/7 cats; cured ~3–9 months	[103]
Feline chronic enteropathy	Allogeneic AD-fMSCs; IV; 2×10^6 cells/kg, 2 times, 2 weeks apart	7 cats in stem cell group; 4 cats in control group	Yes	At 2 weeks and 1 to 2 months; significant improvement or complete resolution of clinical signs in 5/7 cats	[101]

hESC, human embryonic stem cell; FCGS, feline chronic gingivostomatitis; MSC, mesenchymal stem cell; IV, intravenous; AD-fMSC, adipose tissue-derived feline mesenchymal stem cells.

FCGS is a chronic inflammation of the oral mucosa and is associated with a highly reactive immune system [104]. These data support the clinical evidence of immunomodulatory effects of MSCs therapy. To date, compared with autologous MSCs, allogeneic MSCs have shown lower treatment efficacy and delayed clinical response.

In the treatment of refractory GI disease, stem cell transplantations have been actively studied in both human and veterinary medicine. More specified studies on stem cell sources and treatment protocols for each disease may enable innovative clinical applications of stem cells in refractory chronic GI disease in the near future.

STEM CELL TRIALS IN MUSCULOSKELETAL DISEASE

Musculoskeletal disease includes injuries or pain of the joints and tendons, ligaments, muscles, nerves, and accompanying structures, which affect the ability to move. BMSCs are the progenitors for many mesenchymal tissues, such as bone, cartilage and fat [105]. Stem cell-based bone regeneration was evaluated using canine models. Bone defects were induced by surgery and reconstructed using allogeneic mandibular scaffold-loaded and autologous MSCs [105] or β -tricalcium phosphate and autologous BMSCs via the custom-made stem cell-scaffold device [106]. Both studies demonstrated that the use of MSCs accelerated new bone formation in the mandibular or orbital defects, most likely due to increases in the absorption of bone grafts and osteogenesis.

Stem cells are also used in muscle diseases. Duchenne muscular dystrophy is a devastating genetic disorder that induces severe muscle weakness and atrophy in humans [107]. To evaluate therapeutic stem cell efficacy in this incurable form of muscular dystrophy, golden retriever muscular dystrophy (GRMD) dogs were observed clinically as animal models for humans [108-110]. Intra-arterially delivered muscle stem cell [58,95] or mesoangioblasts (vessel-associated stem cells) [110] showed limitations in muscle damage with myofiber regeneration, dystrophin recovery and increased regeneration activity. Thus, these studies concluded that stem cells can provide clinical benefits in GRMD dogs. Few clinical trials related to muscle diseases have been reported [111,112]. Adipose-derived stem cells were injected into 2 dogs with severe skeletal muscle injuries. Clinical improvements and reductions in lesion size were observed after stem cell administration [111]. Semitendinosus myopathy is a rare muscular disorder in certain large breed dogs, and its exact etiology and pathogenesis are still unknown [112]. Because this muscle is responsible for non-weight-bearing positional extension (hip, stifle, and tarsus) and flexion (stifle), lameness and pain are common clinical signs [113]. AD-MSCs treatment of these dogs improved clinical signs without recurrence of lameness, likely due to the prevention of the progression of fibrosis and muscle contracture in semitendinosus myopathy.

Several experimental strategies have provided insight as to whether AD-MSCs therapy can be utilized for the regeneration and maintenance of articular cartilage in osteoarthritis [25,26,114,115]. Administration of autologous AD-MSCs stimulates extracellular matrix synthesis and chondrocyte proliferation and inhibits inflammatory reaction of cartilage [26,114]. In addition, growth factors contained in platelet-rich plasma and hyaluronic acid act as mediators, and potentiators, of the effect of MSCs [26,114]. Significant improvements in limb function, lameness, and force plate gait analysis associated with osteoarthritis observed mostly in the hip joint [22,25,26,114,115], elbow [116], and humeroradial joint [117] (Table 5).

Table 5. Veterinary clinical stem cell trials in musculoskeletal disease

Disease	Cell therapy	No. of dogs	Control	Evaluation periods/effects	Ref.
OA (hip joint)	Autologous AD-MSCs; intraarticular injection; $4.2-5 \times 10^6$ cells	18 dogs divided to stem cell and control group (injection of placebo material)	Yes	At 30, 60, and 90 days; the results showed significantly improved scores for lameness and the compiled scores for lameness, pain, and range of motion.	[22]
OA (hip joint)	Autologous AD-MSCs; intraarticular injection; 30×10^6 cells	9 dogs in stem cell group; 5 healthy dogs in control group	Yes	At 30, 90, 180 days; improvement of limb function in dogs with hip OA was objectively seen.	[25]
OA (hip joint)	Autologous AD-MSCs; intraarticular injection; 30×10^6 cells	8 dogs in stem cell group; 5 healthy dogs in control group	Yes	At 30, 90, 180 days; reduced lameness due to OA was observed after stem cell therapy.	[26]
OA (hip joint)	Autologous AD-MSCs; intraarticular injection; 30×10^6 cells	18 dogs in stem cell group; 17 dogs in PRGF group	Yes	At 1, 3, 6 months; Both groups showed safe and effective outcome and compared to PRGF, cell group showed better results at 6 months.	[114]
OA (hip joint)	Autologous AD-MSCs; intraarticular injection; 30×10^6 cells	10 dogs in stem cell group; 5 healthy dogs in control group	Yes	At 30, 90, 180 days; MSC therapy significantly improved limb function in dogs with hip OA.	[115]
OA (elbow joint)	Autologous AD-MSCs; intraarticular injection; $3-5 \times 10^6$ cells	14 dogs in stem cell group	No	At 30, 60, 90, and 180 days; statistically significant improvement in lameness, range of motion, and pain on manipulation over time was shown.	[116]
OA (humeroradial joint)	Autologous AD-MSCs; intraarticular injection; $3-5 \times 10^6$ cells	4 dogs in stem cell group	No	At 1 week and 1 month; cellular therapy has a significant potential for clinical use inducing functional improvements.	[117]
Skeletal muscle injury	Autologous AD stem cells; case 1, intralesional and IV; 4.7×10^6 cells each, case 2, intralesional 7.5×10^6 cells and IV 3.8×10^6 cells	2 dogs	No	At 19 weeks (case 1) and 22 weeks (case 2); significant reduction in lesion size and clinical improvements	[111]
Semitendinosus myopathy	Autologous AD-MSCs; intralesional and IV	11 dogs in stem cell group	No	At 6 months and 1 year; stem cell treatment helped prevent progression, of the career-ending fibrosis and muscle contracture.	[112]
Gastrocnemius tendon strain	Autologous BMSCs; intralesional; 20×10^6 cells	1 dog	No	At 30, 60, 90, 180, and 365 days; successful functional outcome; incomplete healing with serial orthopedic and ultrasound examinations	[118]
Hip dysplasia	Autologous SVF ($2-5 \times 10^6$ cells) or allogeneic AD-MSCs ($2-8 \times 10^5$ cells); acupuncture point injection	5 dogs in MSC group; 4 dogs in SVF group	No	At 7, 15, and 30 days; clear improvement was observed in both groups.	[24]

SVF, stromal vascular fraction; PRGF, plasma rich in growth factors; AD-MSC, adipose tissue-derived mesenchymal stem cell; MSC, mesenchymal stem cell; BMSC, bone-marrow-derived mesenchymal stem cell; OA, osteoarthritis.

In tendon injuries, autologous BMSCs combination with custom orthosis have great potential for modulating inflammation and stimulating tendon regeneration [118]. After autologous MSCs transplantation, lameness resolved and peak vertical and propulsive forces of contralateral pelvic limb increased. However, incomplete healing was observed via serial orthopedic and ultrasound examinations, so further research is required for clinical application of stem cells in tendon injuries.

Hip dysplasia (HD) is an inherited orthopedic disease that affects dogs of all breeds. Common treatments applied in HD dogs include an energy-restricted diet, exercise-restriction, medical management with analgesics and/or chondroprotective agents, or surgical correction [119]. One study used autologous or allogeneic adipose-derived stem cells in 9 HD dogs [24]. Acupoint was suggested as a stem cell injection site, and stem cell administration resulted in functional improvement and marked decrease in pain on manipulation in 8 dogs with HD. Only one dog showed no remarkable improvements or pathological alterations.

The utility of stem cells in musculoskeletal disease has been actively studied in humans, and preclinical study results using animal models provide useful information for the clinical applications of stem cells in animal disease. The clinical relevance of some disease has been identified, but the pathophysiology, disease process, and treatment responses could vary between species. In addition, preclinical animal study results were overstated due to inappropriate controls and different evaluation methods. Thus, human study results cannot be applied directly to animals, and further research is required.

STEM CELL TRIALS IN NEOPLASIA

According to a previous report [120], cytotoxic chemotherapy has been exploited for a variety of tumor treatments in small animal medicine. These chemotherapy regimens often have limitations due to their dose-dependent toxicities and drug resistance. Thus, over the past decades, veterinary oncologists have searched for novel therapies to achieve a more efficient tumor treatment.

Among them, MSCs transplantation is considered a highly valuable and promising approach for a variety of neoplasia [4]. The positive aspects of MSCs (easily isolated, extensive proliferation, and the differentiation capacity into various cell types) have been previously described in clinical application [16,121]. In addition, genetically modified MSCs can accumulate at the site of cancer and be utilized for cancer gene therapy, which is effective for the cellular delivery of anticancer agents and/or molecules including cytokines, interferons, or pro-drugs that inhibit tumor growth and angiogenesis [122-124]. Gene therapy using genetically modified stem cells has been demonstrated in several human cancer studies. However, few studies have been performed in veterinary medicine.

Canine splenic hemangiosarcoma (HSA) is a highly metastatic malignant tumor, and either splenectomy alone or adjuvant chemotherapy have been considered as the treatments of choice. In one clinical case, human neural stem cells (hNSCs) were used with 5-fluorocytosine in a dog with HSA lung metastasis [125]. Significant reduction in the size and number of metastatic lung nodules with fewer side effect was observed 2 weeks after the hNSCs were treated with 5-fluorocytosine. The injected hNSCs had been engineered to express the cytosine deaminase gene, which can converts the prodrug 5-fluorocytosine into the active form. This led to a significant size reduction of the metastatic lung nodules [126]. In addition, hNSCs delivered an anticancer agent to the neoplasm, including the metastatic lesions. Another study demonstrated the use of MSCs combined with recombinant human bone morphogenetic protein 2 (rhBMP-2) and chemotherapeutic agents in a canine osteosarcoma model [127]. The results showed that the MSCs/rhBMP-2/chemotherapeutic agent's injected groups experienced more effective tumor size reduction and neoplastic cell infiltration than the conventional treatment group. This preliminary test result indicates the potential for a promising new modality in cancer treatment, but further studies and clinical trials are necessary.

In the aspects of hematological tumor, leukemia and lymphoma have been considered a refractory malignant neoplasia, even though several chemotherapy protocols have been known [128]. Suter et al. [129] reported the first clinical case of suspected acute lymphocytic leukemia treatment with allogeneic hematopoietic cell transplantation (HCT) with dog leukocyte antigen-matched CD34+ cells (from related siblings). Because acute leukemias

are rare aggressive neoplasms of immature lymphopoietic or hematopoietic progenitor cells, the prognosis is poor and treatment outcomes are limited. The dog in this study presented favorable clinical outcomes within the 2-year follow-up period, and this pilot case report provides valuable clinical possibilities for the use of allogeneic HCT in dogs. Lymphoma is a well-recognized lymphoid origin neoplasm in dogs. Canine T-cell lymphoma has a poorer prognosis than that of B-cell lymphoma, and the median survival time is 6–9 months and 8–16 months with multiagent chemotherapy, respectively [130]. Two clinical trials used apheresis and peripheral blood HCT (PBHCT) in canine B- and T-cell lymphoma [131,132]. Both studies used CD34+ cells after total body irradiation as a treatment for lymphoma and recommended PBHCT in B- and T-cell lymphoma as a valuable alternative treatment (Table 6).

Because of the natural occurrence and biological similarities of cancer in animals and humans, the field of comparative oncology would benefit from a focus on companion animals for the development of new cancer therapy. Few therapeutic approaches for spontaneous cancer in dogs have revealed promising effects of treatment with stem cells. However, the utility of stem cells for targeted cancer therapy is still vague in veterinary medicine due to the low number of clinical studies and the unclear mechanisms of action.

FUTURE DIRECTIONS FOR VETERINARY CLINICAL STEM CELL TRIALS

Regenerative medicine is an emerging field in both human and veterinary medicine. Dogs have been usually used in experimental models and preclinical studies for stem cell treatments in humans. The need for stem cell treatment has expanded in veterinary medicine, and clinical applications are being continuously attempted.

This study reviewed 6 clinical categories of stem cell application in clinically ill dog and cats. Among them, major progress in stem cell application has been made in the field of neurology and musculoskeletal disease. The most promising results were found by studies conducted on spinal cord injuries and osteoarthritis using autologous MSCs from bone marrow- or adipose tissue. Some of the studies provided controls for more efficient evaluations, but treatment frequency, interval, and stem cell dosages varied, making it difficult to generalize the application. Other clinical trials looking at tissue and organ repair/regeneration effects of stem cells were conducted

Table 6. Veterinary clinical stem cell trials in neoplasia

Disease	Cell therapy	No. of dogs	Control	Evaluation periods/effects	Ref.
Hemangiosarcoma with pulmonary metastasis	hNSCs; IV; 1×10^7 cells	1 dog (stem cell injection with 5-fluorocytosine therapy about 30 days after surgery)	No	Follow-up until the patient died (105 days); hNSCs/5-FC therapy can improve the quality of dog's life with therapeutic effects and lower side effects	[125]
Acute large granular lymphocytic leukemia	Allogeneic PBHCT; IV; 5×10^6 CD 34+ cells/kg	1 dog	No	Follow-up for 2 years; considerable clinical benefit over chemotherapy alone.	[129]
T-cell lymphoma	Autologous PBHCT; IV; more than 2×10^6 CD 34+ cells/kg	15 dogs in stem cell group	No	Follow-up for overall survival of median 239.5 days (range, 4–738 days); PBHCT may be considered as a treatment option for dogs with T-cell lymphoma.	[131]
B-cell lymphoma	Autologous PBHCT; IV; more than 2×10^6 CD 34+ cells/kg	24 dogs in stem cell group	No	Follow-up for assessment of disease-free interval (median 271 days) and overall survival (median 463 days); PBHCT may be considered as a treatment option for dogs with B-cell lymphoma.	[132]

hNSC, human neural stem cell; IV, intravenous; PBHCT, peripheral blood hematopoietic cell transplantation.

for the treatment of skin or muscle wounds. The results of these studies were also favorable, but they failed to demonstrate objective indicators with only a few clinical cases. Because of the immunomodulatory capacity and paracrine role of some types of stem cells, clinical trials were performed on immune-mediated inflammatory disease such as meningoencephalitis, AD, IBD, anal furunculosis, and FCGS. However, understanding the exact mechanisms of cell therapy for each disease requires further study. In addition, more cases that have clinical, scientific controls and long-term follow-up are needed. Stem cells for the treatment of cancer is an emerging modality in humans, but there is a lack of clinical application in veterinary medicine for evaluation.

Because standardized treatment and evaluation methods (including case selection, optimal cell type, delivery route, time of administration, cell dose, evaluation methods, and periods) are not optimized for each trial, treatment efficacy is uncertain and there are always questions that remained unanswered. To use stem cells in clinical therapy, 'safety' and 'efficacy' are the 2 main issues to consider. In human medicine, there are regulations and guidelines for using stem cell-based products for clinical and commercial use [133].

The basic principles for using cell-based products in veterinary clinical trial should include:

- 1) Donor selection criteria
 - The donor should be screened for infectious diseases and other risk factors to prevent the transmission of disease agents.
- 2) Quality-controlled cells
 - The origin of the cells, conditions for storage, composition of the products should be adequately defined and labeled.
 - Demonstration that cellular function and integrity have been preserved.
 - Prove free of contamination from viruses, bacteria, fungi, mycoplasma and endotoxins.
- 3) Efficacy and safety
 - The efficacy and safety of the cells after delivery have been demonstrated in target animals.
 - Long-term safety evaluation is highly recommended.
 - Adverse events after stem cell intervention should be reported.
 - Consider risk factors such as toxicity, tumorigenicity, and immune reactions.

Recently, the United States Food and Drug Administration (FDA) and the European Medicine Agency's (EMA) approved guidance for cell-based products for veterinary use [133-135]. In 2018, the Animal and Plant Quarantine Agency (APQA) of Korea also documented 'Guideline on safety assessment of cell-based products for animal use' [136]. If researchers and clinicians follow the guidelines of FDA, EMA, and APQA of Korea on the above 3 principles, the problems of standardized treatment protocols and evaluation methods of stem cell therapy will be rapidly improved.

Based on the previous pilot and preliminary studies, clinicians' and researchers' efforts to standardize stem cell treatments are needed. In addition, further preclinical and clinical stem cell studies are necessary for the progress of this treatment modality in both human and veterinary medicine.

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