Healthy Blue

Medical Policy

Subject:	Therapeutic use of Stem Cells, Blood and Bone Marrow Products		
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Description/Scope

This document addresses uses of stem cell therapy for the prevention and treatment of health conditions, including but not limited to, peripheral vascular disease, and orthopedic, autoimmune, inflammatory, and degenerative conditions. Stem cell therapy involves the use of stem cells (usually in the form of an injection or infusion) to repair damaged cells and body tissues. The document also addresses the use of autologous cell therapy using, but not limited to the use of, skeletal myoblasts, endothelial progenitor cells (EPCs), and bone marrow mononuclear cells (BMMC) for the treatment of a wide variety of conditions, including damaged myocardium. In addition, autologous blood derived wound products, platelet rich plasma (PRP), and autologous protein solution for the treatment of skin wounds, various musculoskeletal injuries, and during various surgical procedures are addressed.

This document ***does not address***: stem cell therapy used for disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment (including transplantation of autologous or allogeneic stem cells), or autologous hematopoietic stem cell-based gene therapy. FDA-approved stem cell products are listed on the FDA website here: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products.

Note: Please be aware that use of recombinant human platelet-derived growth factor (becaplermin [Regranex®]) or bioengineered autologous skin-derived products (for example, SkinTE™, MyOwn Skin™) *are not* addressed in this document.

Note: This document does *not* address therapeutic uses of stem cells for hematopoietic indications (FDA-approved products derived from stem cells that are approved for limited use in individuals with disorders involving the hematopoietic system).

First identified in the hematopoietic system, stem cells are likely to be present in many other tissues. Stem cells can be derived from human embryos or somatic tissues in the adult or they can be created by inducing greater potency in an already differentiated somatic cell. Examples of adult stem cells (also called somatic stem cells or tissue-specific stem cells) not used for hematopoietic indications include, but are not limited to, mesenchymal (also called stromal stem cells), neural, epithelial, epidermal, and follicular. Extraction sources of adult stem cells include, but are not limited to, blood, bone marrow, adipose tissue, umbilical cords, placentas, and amniotic fluid. Other types of stem cells transplanted include peripheral bone marrow mononuclear cells [PBMNCs], and bone marrow mononuclear cells [BMMNCs].

Notes:

- This document *does not* address mesenchymal stem cells as an adjunct to spinal fusion or surgical procedures involving bone.

- For additional information on related topics, please see the following:
  - MED.00110 Silver-based Products for Wound and Soft Tissue Applications
  - MED.00132 Adipose-derived Regenerative Cell Therapy and Soft Tissue Augmentation Procedures
  - SURG.00011 Allogeneic, Xenographic, Synthetic, Bioengineered, and Composite Products for Wound Healing and Soft Tissue Grafting

Position Statement

Investigational and Not Medically Necessary:

I. Stem cell therapy, including but not limited to mesenchymal stem cell therapy is considered **investigational and not medically necessary** for the prevention and treatment of all conditions, including but not limited to:
   A. Peripheral vascular disease; **or**
   B. Orthopedic conditions; **or**
   C. Autoimmune conditions; **or**
   D. Inflammatory conditions; **or**
   E. Degenerative conditions.

II. Autologous cell therapy, including but not limited to, skeletal myoblasts, mesenchymal stem cells, endothelial progenitor cells (EPCs) or bone marrow mononuclear cells (BMMC), is considered **investigational and not medically necessary** for all indications, including but not limited to treatment of damaged myocardium**.**

III. Autologous blood-derived wound products (for example, Aurix [formerly Autologel], Vitagel) are considered **investigational and not medically necessary** for all applications.

IV. Use of platelet rich plasma (PRP), including autologous conditioned plasma (ACP), is considered **investigational and not medically necessary** for all indications, including the treatment of any of the following:
   A. Cutaneous wounds; **or**
   B. Soft tissue injuries (including epicondylitis and sinus surgery); **or**
   C. Bone injuries (including surgically created wounds and non-unions).

V. Use of bone marrow aspirate concentrate (BMAC) is considered **investigational and not medically necessary** for all indications, including for the treatment of critical limb ischemia.

VI. Use of autologous protein solution (for example, nSTRIDE®), also known as autologous white blood cell concentrate, is considered **investigational and not medically necessary** for all indications.

Note: This document *does not* address stem cell therapy used for disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment, or hematopoietic stem cell transplantation.

Rationale

Mesenchymal Stem Cell Therapy

Orthopedic Conditions

Surgical repair of tendon, ligament, cartilage and bone defects has been the standard therapy, which may be augmented by autologous grafts, cadaveric allografts or synthetic grafts. However, there have been several limitations to the use of grafts in orthopedic therapy. For instance, autologous graft sources may be hampered by comorbid conditions, limited sites suitable for harvesting, and the potential of graft failure. Alternative regenerative technologies, which could minimize or avoid these issues while regenerating damaged tissue are being actively investigated.

Various agents and techniques to procure and expand mesenchymal stem cells (MSCs) to achieve sufficient numbers for infusion or implantation are being studied and implemented in proprietary processes for diverse orthopedic indications. The processing of cadaveric allogeneic donor MSCs typically involves proprietary techniques and a combination of MSCs with various transport mediums. In addition, it is not clear that MSCs procured from different tissue sources are functionally equivalent. There is a paucity of randomized controlled trials in humans to support the safety and efficacy of using MSC therapy for orthopedic indications, including cartilage and ligament repair and bone regeneration.

At this time, the medical evidence supporting the use of MSCs for orthopedic indications involving the cartilage or ligaments is limited to pre-clinical studies, case series and small, randomized controlled trials. The efficacy and safety of these novel therapies have not been established in well-designed, large randomized controlled trials with long-term follow-up.

Several preclinical studies have been conducted to evaluate the effectiveness of MSCs in tissue regeneration. Caudwell and colleagues (2014) conducted a systematic review of preclinical studies using MSC and scaffolds in the treatment of knee ligament regeneration. The authors concluded, based on their investigation of 21 articles, that preclinical evidence of ligamentous regeneration with MSC and scaffold use was established, but limited clinical evidence exists to support recently developed scaffolds. Furthermore, no consensus has been reached on the nature of scaffold material that is most suitable.

A systematic review of preclinical studies published by Haddad and colleagues (2013) reviewed 19 articles that had used cell-based approaches to tissue-engineered menisci; cell types used included MSCs amongst others. The authors stated that, “The diversity of studies made it impossible to adhere to full guidelines or perform a meta-analysis,” but concluded that overall superior tissue integration and favorable biochemical properties were observed in regenerated tissues when compared to acellular techniques.

In 2011, Wakitani reported long-term follow-up of 45 articular cartilage repairs utilizing autologous bone marrow-derived MSCs (BMSCs) in 41 individuals. With a mean follow-up of 75 months (5 to 137 months), the authors reported no tumors or infections observed in the individuals who were treated between 1998 and November 2008. Although considered a low risk, the authors concluded that, “The possibility that the cells transplanted in joints move and injure other parts of the body remains unresolved” (Wakitani, 2011)

A pilot study was conducted by Wakitani and colleagues (2004) using autologous bone MSC therapy to repair nine full-thickness cartilage defects in the patello-femoral joints of 3 individuals. The assessment of clinical symptoms were rated with the International Knee Documentation Committee Subjective Knee Evaluation Form (IKDC score), with 0 being the worst and 100 being the best rating. IKDC scores improved for all 3 individuals during the follow-up period ranging from 7 to 20 months after receiving mesenchymal therapy. In all 3 cases, the investigators were unable to confirm the material covering the defects was in fact hyaline cartilage resulting from mesenchymal cell therapy.

In a systematic review by Longo and colleagues (2011), authors state that the use of MSC therapy for repair of tendon injuries is "At an early stage of development. Although these emerging technologies may develop into substantial clinical treatment options, their full impact needs to be critically evaluated in a scientific fashion."

In 2012, Lee and colleagues conducted a prospective, short-term comparative study to determine if knees with symptomatic cartilage defects treated with outpatient injections of MSCs and hyaluronic acid (HA; n=35) had better outcomes than an open-air implantation of MSCs (n=35). The outcome of interest was the International Cartilage Repair Society (ICRS) Cartilage Injury Evaluation Package and MRI results 1 year post-procedure. No adverse events were reported and significant improvement was seen across several domains of the ICRS evaluation package at final follow-up (mean 24 months). Although MRI results were promising, authors acknowledge that the sensitivity of MRIs in lesion identification was only estimated at 45%. A shortcoming of this study, aside from the small sample size and short-term data, is the inability to distinguish the MSC effect on outcomes from the HA effect since the control group received neither.

In 2013, Wong and colleagues conducted a randomized controlled trial (RCT) evaluating 56 participants with unicompartmental, osteoarthritic, varus knees enrolled in either the stem cell recipient group (n=28) or the control group (n=28). The treatment group received intra-articular injections of MSCs and HA 3 weeks post-surgical intervention and the control group received HA only. Participants were re-evaluated at 6-, 12- and 24-month follow-up. The treatment group showed significantly better scores than the control group in Tegner ($p=0.021$), Lysholm ($p=0.016$), and IKDC ($p=0.01$) scores. MRI scans at 1 year follow-up showed significantly better Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) scores ($p<0.001$). Authors concluded that the investigated intervention demonstrated efficacy in short-term clinical and MOCART outcomes. However, data was insufficient to demonstrate clinical improvement and long-term efficacy and safety data.

In 2014, Vangsness and colleagues performed the first randomized, double-blind controlled clinical trial investigating the efficacy and safety of MSCs in the treatment of an orthopedic indication. A total of 55 participants from seven institutions who were eligible for a partial medial meniscectomy were enrolled and randomized into one of three treatment groups: Group A (n=17) received an injection of $50x10^6$ allogeneic MSCs; Group B (n=18), received $150x10^6$ MSCs; and the control group (n=19) received an HA injection only. Outcomes of interest at intervals over the 2-year follow-up period included safety, meniscus regeneration, overall knee joint condition and clinical outcomes. No adverse events occurred and investigators found a significant increase in meniscal volume ($p=0.022$; determined by MRI) in both Groups A and B; no participants met the threshold for increased volume (15%) in the control group. Furthermore, both groups A and B reported a significant reduction in pain compared to the control group. Results of this small, Phase I/II clinical trial are promising for use of MSCs in knee-tissue regeneration. Data from larger trials are needed to confirm the early results.

Vega and colleagues (2015) conducted a small, randomized, controlled trial comparing intra-articular injections of allogeneic bone marrow MSCs and HA in individuals with knee osteoarthritis (n=30). Each participant received either one injection of MSC or HA and were followed for 1 year. Assessed outcomes included evaluations of pain, disability, quality of life and articular cartilage quality as determined by MRI. The MSC group reported a medium to large treatment effect (effect size, 0.58-1.12) while the HA group reported a small treatment effect (effect size, 0.19-0.48). While the MSC group reported improved results over the HA group, it is noted that this is the first study to demonstrate the feasibility, safety and efficacy of the use of allogeneic MSCs in treating osteoarthritis. The authors note that further research is needed on how MSCs "relieve pain, promote regeneration, and become immune evasive."

Jo and colleagues (2017) reported the results of a 2-year follow-up study that evaluated the safety and effectiveness of intra-articular injections of adipose tissue-derived MCSs (AD-MCSs) for the treatment of osteoarthritis of the knee. A total of 18 subjects with osteoarthritis of the knee were enrolled (15 female; 3 male; mean age, 61.8 ± 6.6 years [range, 52-72 years]). Participants in the low-, medium-, and high-dose groups received an intra-articular injection of 1.0×10^7, 5.0×10^7, and 1.0×10^8 AD MSCs into the knee, respectively. Clinical and structural evaluations were conducted using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and measurements of the size and depth of the cartilage defect, signal intensity of regenerated cartilage, and cartilage volume MRI. No treatment-related adverse events were reported during the 2-year period. An intra-articular injection of autologous AD MSCs enhanced knee function, as measured with the WOMAC, Knee Society clinical rating system (KSS), and Knee injury and Osteoarthritis Outcome Score (KOOS), and decreased knee pain, as measured with the visual analog scale (VAS), for up to 2 years regardless of the cell dosage. However, statistical significance was seen primarily in the high-dose group. Clinical outcomes tended to decline after 1 year in the low- and medium-dose groups, whereas those in the high-dose group remained level until 2 years. The structural outcomes gauged with MRI also showed similar trends. The authors concluded that this study demonstrated the safety and efficacy of the intra-articular injection of AD-MSCs into the osteoarthritic knee over 2 years. The authors acknowledged that this study highlighted potential concerns about the durability of clinical and structural outcomes and encouraged larger randomized clinical trials.

Ha and colleagues (2019) conducted a systematic review assessing the efficacy of intra-articular MSCs in terms of clinical outcomes including pain and function and cartilage repair in individuals with osteoarthritis of the knee. Clinical outcomes were evaluated using clinical scores, and cartilage repair was assessed using magnetic resonance imaging and second-look arthroscopy findings. A total of 17 studies met the inclusion criteria: 6 randomized controlled trials; 8 prospective observational studies; and 3 retrospective case-control studies. Of the 17 studies, 1 used umbilical cord blood-derived MSCs, 2 used adipose tissue-derived MSCs, 6 used adipose tissue-derived stromal vascular fraction and 8 studies used bone marrow-derived MSCs. All studies except for 2 reported improved clinical outcomes at final follow-up or significantly better clinical outcomes in the MSC group. With regard to cartilage repair, 9 of 11 studies reported an improvement in the state of the cartilage on magnetic resonance imaging. A total of 6 of 7 studies reported the presence of repaired tissue on second-look arthroscopy. The authors concluded that in many cases, intra-articular MSCs improve pain and function in knee osteoarthritis at short-term follow-up (< 28 months), however, the evidence of efficacy of intra-articular MSCs on both cartilage repair and clinical outcomes remains limited.

Although preclinical studies, case series, and small randomized trials suggest that MSC therapy may improve regeneration of bone or tissue in orthopedic indications, the lack of validated, comparable scoring, robust sample sizes and long-term follow-up data preclude definitive conclusions regarding the net health benefit of MSC therapy in the treatment of orthopedic conditions.

In 2020, the American College of Rheumatology (ACR) and the Arthritis Foundation (AF) released a joint guideline on the management of osteoarthritis of the hand, hip, and knee. The ACR and AF strongly recommend against stem cell injections in individuals with knee or hip osteoarthritis stating "there is concern regarding the heterogeneity and lack of standardization in available preparations of stem cell injections, as well as techniques used" (Kolasinski, 2020). In regards to hand osteoarthritis, no recommendation was made due to a lack of studies evaluating stem cell therapy as a treatment (Kolasinski, 2020).

Neurodegenerative Diseases

Alzheimer's Disease

Kim and colleagues (2015) conducted a phase I clinical trial in individuals (n=9) with mild-to-moderate Alzheimer's disease to evaluate the safety and dose-limiting toxicity of stereotactic brain injection of human umbilical cord blood-derived MSCs (hUCB-MSCs). The low- (n=3) and high-dose (n=6) cohorts received a total of 3.0×10^6 cells/60 μL and 6.0×10^6 cells/60 μL, respectively, into the bilateral hippocampi and right precuneus. None of the study participants demonstrated serious adverse reactions during the 24-month follow-up period. During the 12-week follow-up period, the most frequent acute adverse event was wound pain from the surgical procedure (n=9), followed by headache (n=4), dizziness (n=3), and postoperative delirium (n=3). No dose-limiting toxicity was reported. The authors concluded that the administration of hUCB-MSCs into the hippocampus and precuneus by stereotactic injection was feasible, safe, and well tolerated but additional trials are warranted to determine treatment efficacy.

Amylotrophic lateral sclerosis (ALS)

Mazzini and colleagues (2003) evaluated the feasibility and safety of a method of intraspinal cord implantation of autologous MSCs in 7 participants (4 females and 3 males; range: 23–74 years, mean age 46.6 ± 16.8 years) with ALS. The group had severe functional impairment of the lower limbs and mild functional impairment of the upper limbs without signs of respiratory failure. Participants were monitored by clinical evaluation which included the Norris score, ALS-FRS scale, bulbar score, and MRC strength scale. Respiratory assessment included clinical evaluation, arterial blood gas analysis, pulmonary function tests and nocturnal cardio-respiratory monitoring. The neurophysiological assessments consisted of somatosensory evoked potentials (SEP) and EMG. The neuro-radiological assessment included MRI of the spinal cord and brain before and after gadolinium DTA infusion. A clinical psychologist conducted a psychological evaluation. None of the participants experienced severe adverse events such as death, respiratory failure or permanent post-surgical neurological deficits. Minor adverse events included intercostal pain (n=4) which was reversible after a mean period of 3 days (range: 1–6) after surgery, and leg sensory dysesthesia (n=5) which resolved after a mean period of 6 weeks (range: 1–8) following surgery. None of the participants manifested bladder and bowel dysfunction, or leg motor deficit. There were no anesthetic complications. MRI with gadolinium DTA infusion carried out at 3 and 6 months post implantation demonstrated no evidence of structural changes of the spinal cord or signs of abnormal cell proliferation when compared with the

baseline. SEPs from tibial nerve stimulation demonstrated a mild delay of the central conduction time 3 days after surgery but this normalized within 1 month following transplantation. All of the participants showed a good acceptance of the procedure and no significant modifications of the quality of life or the psychological status were observed. In all of the participants, muscular strength (MRC scale) declined during the 6 months before transplantation. However, at the third month post stem cell implantation a trend towards a slowing down of the linear decline of muscular strength was evident in 4 participants in the proximal muscle groups of the lower limbs, while a mild increase in strength was observed in the same muscle groups of 2 participants. While the authors concluded that the study seemed to demonstrate MSC transplantation into the spinal cord of humans is safe and well tolerated by individuals with ALS, the authors stated that additional controlled studies are needed to evaluate the efficacy of stem cell therapy in the treatment of ALS.

Parkinson's Disease

Research exploring the feasibility of MSC transplantation as a treatment of Parkinson's disease is ongoing. In one study (NCT00976430), researchers investigated the safety and efficacy of autologous MSCs in treating advanced Parkinson's disease by harvesting and processing the stem cells from bone marrow and transplanting them via stereotactic techniques into the striatum of the subject. However, the study was terminated because an adequate number of participants could not be recruited in the set timeframe. Other studies exploring the use of MSCs as a treatment of Parkinson's disease are ongoing but not yet completed or published. Information regarding these studies is available on the clinicaltrials.gov web site.

At this time, there is insufficient evidence from well-designed clinical trials to evaluate the clinical utility of MSC therapy in individuals with neurodegenerative diseases.

Autoimmune Diseases

Celiac Disease

Ciccocioppo and colleagues (2016) reported the results of a study that investigated the feasibility, safety, and efficacy of serial infusions of autologous bone marrow-derived MSCs in a 51-year-old woman with type II refractory celiac disease. MSCs were separated, expanded, and characterized according to standard protocols. The researchers monitored the participant's malabsorption indexes, mucosal architecture, and percentage of aberrant intraepithelial lymphocytes during study enrollment, at each infusion, and 6 months post treatment. Mucosal expression of interleukin (IL)-15 and its receptor was also monitored. The subject underwent 4 systemic infusions of 2×10^6 MSCs/kg body weight 4 months apart without adverse effects. During the treatment period, the participant experienced gradual and durable amelioration of her general condition, with normalization of stool frequency, body mass index, laboratory test results, and mucosal architecture. The expression of IL-15 and its receptor practically disappeared. At this time, there is insufficient evidence from well-designed clinical trials to evaluate the clinical utility of MSC therapy in individuals with celiac disease.

Multiple sclerosis

In a triple-blind, placebo-controlled study, Fernandez and colleagues (2018), investigated the safety and feasibility of the use of adipose-derived MSCs for the treatment of secondary-progressive multiple sclerosis. The cell samples

were obtained from consenting participants by lipectomy and subsequently expanded. Study participants were randomized 1:1:1 to an intravenous (IV) infusion of placebo or one of two dose-groups ($1x10^6$ cells/kg or $4x10^6$ cells/kg). The study was triple blinded (the treating physician, study participant and statisticians were unaware of treatment assignment). Participants were followed for 12 months. The researchers monitored safety using laboratory parameters, vital signs and spirometry. EDSS, MRI and other measures of possible treatment effects and adverse events were also recorded. A total of 34 subjects underwent lipectomy for adipose-derived MSC collection, were randomized and 30 were infused (11 placebo, 10 low-dose and 9 high-dose); 4 randomized participants were not infused due to karyotype abnormalities in the cell product. Measures of treatment effect demonstrated an inconclusive trend of efficacy. The mean EDSS score and the individual EDSS did not reflect any significant changes over the course of the study. Baseline MRI data was similar between the three groups. The researchers reported some non-statistically significant differences between the placebo and treatment groups for the evoked potentials parameters after 12 months of treatment. Tibial SEP central conduction time (N22-P39) and the motor evoked potential (MEP) central conduction time for the legs, reflected statistically significant diminishing latencies over time in placebo and the two treatment groups, but these differences were not statistically significant comparing placebo and both treatment groups. Visual evoked potential (VEP) and median nerve SEP (N13-N20) also demonstrated a trend of stabilization or amelioration of latencies over time in treatment groups, however, these differences did not reach statistical significance over the time. There were no significant changes in the cerebral spinal fluid from baseline to the 12-month follow-up. One serious adverse event was reported in the treatment arms (urinary infection, considered not related to study treatment). No other changes in safety parameters were reported. Although the results of the study did not demonstrate treatment efficacy, the authors found infusion of autologous adipose-derived MSCs safe and feasible in individuals with secondary-progressive multiple sclerosis.

Systemic Lupus Erythematosus (SLE)

Wang and colleagues (2014) conducted a multicenter clinical trial to assess the safety and efficacy of allogeneic umbilical cord MSC transplantation (MSCT) in subjects with active and refractory SLE. Researchers recruited 40 individuals with active SLE from four clinical centers. Allogeneic umbilical cord MSCs were infused intravenously on days 0 and 7. The primary endpoints were safety profiles. The secondary endpoints included major clinical response (MCR), partial clinical response (PCR) and relapse. Each participant was re-assessed at 1, 3, 6, 9 and 12 months post MSC transplantation. Evaluations performed at the follow-up visits included a physical examination, determination of Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score, British Isles Lupus Assessment Group (BILAG) analysis, serologic studies and evaluation of organ function. A total of 39 subjects (39/40, 97.5%) underwent umbilical cord MSC infusions twice with an interval of 1 week, and 1 participant (1/40, 2.5%) was exempted from the second MSC infusion due to uncontrolled disease progression. The overall survival rate was 92.5% (37 of 40 subjects). Umbilical cord MSCT was well tolerated, and no adverse events related to the transplantation were observed. During the 12 months of follow-up, an MCR was achieved in 13 participants (32.5%) and 11 participants (27.5%) achieved a PCR. Three individuals (12.55%) experienced disease relapse at 9 months and 4 participants (16.7%) experienced disease relapse at 9 months after a prior clinical response. The SLEDAI scores decreased significantly at 3, 6, 9 and 12 months follow-up. Total BILAG scores decreased at 3 months and continued to decrease at subsequent follow-up visits. BILAG scores for hematopoietic, renal and cutaneous systems improved. Among participants with lupus nephritis, 24-hour proteinuria diminished after transplantation, with statistically significant differences at 9 and 12 months. Serum creatinine and urea nitrogen declined to the lowest level at 6 months, but these values slightly increased at 9 and 12 months in 7 relapse cases. Additionally, serum levels of albumin and complement 3 rose after MSCT, peaked at 6 months and then slightly

declined by the 9- and 12-month follow-up examinations. Serum antinuclear antibody and anti-double-stranded DNA antibody diminished after MSCT, with statistically significant differences at 3-month follow-up examinations. The authors concluded that the study results demonstrate that umbilical cord MSCT is a safe and effective treatment for individuals with SLE, but a repeated MSC infusion may be necessary after 6 months to avoid disease relapse. The authors also acknowledge that limitations of the study include its lack of a randomized controlled design and the lack of uniformity amongst the condition of the study participants.

In 2015, Wang and colleagues reported the results of a study that investigated whether double transplantations of MSCs is superior to single transplantation. Of the 58 refractory SLE subjects enrolled in the study, 30 were randomly given single MSCT, and the other 28 were given double MSCT. Participants were followed to determine rates of survival, disease remission, and relapse, as well as transplantation-related adverse events. Serologic features and changes in the SLEDAI were monitored. At more than 1 year follow-up, the results demonstrated that no remarkable differences between single and double allogeneic MSCT were found in terms of disease remission and relapse, amelioration of disease activity and serum indexes. This study demonstrated that single MSC transplantation at the dose of one million MSCs per kilogram of body weight was sufficient to induce disease remission for refractory SLE subjects. Although 95% of the participants had lupus nephritis at the time of enrollment, it is unclear whether MSC therapy can ameliorate renal pathology, aside from the improvements in renal function, because the pathological data on the participants at the time of enrollment was not available.

Crohn's Disease

In a Phase I trial, Duijvestein and colleagues (2010) assessed the safety and feasibility of the use of autologous bone marrow-derived MSC treatment for luminal Crohn's disease refractory to steroids and immunomodulators. A total of 10 adult participants with refractory Crohn's disease underwent bone marrow aspiration under local anesthesia. Bone marrow MSCs were isolated and expanded ex-vivo. MSCs were assessed in- vitro for functionality and phenotype. Nine participants received two doses of $1\text{-}2\times10^6$ cells/kg body weight, intravenously, 7 days apart. During follow-up, the participants were monitored for possible side effects and changes in the Crohn's disease activity index (CDAI). Colonoscopies were conducted at weeks 0 and 6, and mucosal inflammation was assessed using the Crohn's disease endoscopic index of severity. The study demonstrated a decline in CDAI by ≥ 70 from baseline in 3 participants at 6 weeks post treatment; conversely 3 participants required surgery due to worsening Crohn's disease. None of the participants achieved remission. The subjects reported minor allergic reaction (10%), headache (30%), as well as taste and smell disturbances (90%) which were considered related to MSC infusion.

Zhang and colleagues (2018) investigated the efficacy and safety of umbilical MSCs for the treatment of Crohn's disease. The Phase III clinical trial included 82 participants who were diagnosed with Crohn's disease and had received steroid maintenance therapy for more than 6 months. A total of 41 participants were randomly selected to receive four peripheral IV infusions of 1×10^6 umbilical cord MSCs/kg, with one infusion per week. Participants were followed for 12 months. Assessment tools included the CDAI and Harvey-Bradshaw index (HBI). Corticosteroid dosage was also assessed. Twelve months post treatment, the CDAI, HBI, and corticosteroid dosage had decreased by 62.5 ± 23.2, 3.4 ± 1.2, and 4.2 ± 0.84 mg/day, respectively, in the umbilical cord-MSC group and by 23.6 ± 12.4, 1.2 ± 0.58, and 1.2 ± 0.35 mg/day, respectively, in the control group ($p<0.01$, $p<0.05$, and $p<0.05$ for UC-MSC vs control, respectively). Fever after the administration of MSC infusion was reported in 4 participants. No serious adverse events were reported. The authors concluded that umbilical cord-MSCs were an

effective treatment for Crohn's disease that produced mild side effects. A limitation of this study was that it did not examine indicators of immune status or intestinal histopathology in the participants. Therefore, the mechanism by which stem cell therapy modifies Crohn's disease remains unclear.

While small, preliminary studies investigating the use of MSC therapy as a treatment for Crohn's disease may show promise, additional well-designed studies with larger populations and longer follow-up periods are needed before conclusions regarding the safety and efficacy of MSC therapy can be made.

Steroid-Refractory Acute Graft Versus Host Disease

Remestemcel-L (Ryoncil™) (Mesoblast, New York, NY) is a preparation of adult MSCs specially formulated for intravenous infusion currently under investigation. The therapy is designed to modulate the immune system for the treatment of children with steroid-refractory acute graft versus host disease (SR-aGVHD). Remestemcel-L was granted Fast Track Designation and Biologic License Application (BLA) Priority Review from the U.S. Food and Drug Administration (FDA) based on new clinical information submitted to the FDA. To date, in the U.S there are no FDA approved treatments for children under 12 with SR-aGVHD.

Summary

MSCs isolated from bone marrow and other sites, display specific anti-inflammatory and immunomodulation properties and may be a tool for the treatment of various chronic diseases. While the results of some early trials have been promising, a number of questions remain (Goldberg, 2017; Viganò, 2016). The available data have not yet established that MSCs, when infused or transplanted, can regenerate by incorporating themselves into native tissue, survive, differentiate, and promote the preservation of injured tissue. In addition, the optimal source for MSCs has not been clearly identified. Randomized, controlled trials that are adequately powered and include long-term follow-up data are needed before conclusions regarding the safety, efficacy and clinical utility of MSC therapy for the treatment of chronic autoimmune, inflammatory, orthopedic and degenerative diseases can be made.

Bone Marrow Mononuclear Cell and Peripheral Blood Mononuclear Cell Therapies

Peripheral Vascular Disease

The use of autologous or allogeneic stem cell therapy as a treatment of peripheral vascular disease (PVD) has been the subject of many peer-reviewed published articles. Most of the available evidence is in the form of small case series studies with less than 30 subjects (Bartsch, 2006, 2007; Durdue, 2006; Huang, 2004; Kawamoto, 2009; Lara-Hernandez, 2010; Van Tongeren, 2008). There are a few studies with greater than 100 participants, but as with the smaller studies, most use case series methodology (Horie, 2010; Matoba, 2008). The studies themselves vary in follow-up duration, specific method of transplantation (for example, IV, intramuscular [IM], and intra-arterial [IA]), type of stem cells transplanted (PBMNCs, BMMNCs, or MSCs), and underlying etiology of the vascular disease (for example, diabetes, thromboangiitis obliterans [TAO], arteriosclerosis obliterans [ASO]). Additionally, some studies are limited to the treatment of lower limb PVD, while others include subjects with upper limb PVD as well. These case series tend to report positive impact of stem cell therapy with rare transplantation-related complications. However, there are significant concerns about these case series, which are prone to publication bias (only positive case series published) as well as the lack of prospective, randomized comparison groups.

Several nonrandomized trials have been reported for autologous stem cell treatments (Higashi, 2004; Katamata, 2007). Ondara and colleagues (2011) reported a study that was a re-analysis of data previously published by Horie (2010) and Matoba (2008). The authors reported that after adjustment for history of dialysis and Fontaine class, there were no significant differences between the treatment with BMMNC compared to PBMNC with respect to overall survival or amputation-free survival. They also reported that the negative prognostic factors affecting overall survival or amputation-free survival were the number of CD34-positive cells collected, history of dialysis, Fontaine class, male sex, and older age.

A double-blind placebo-controlled RCT has been published on the use of allogeneic stem cell therapy to treat PVD (Gupta, 2015). This small study involved 20 subjects with critical limb ischemia (CLI) who were unable to undergo traditional revascularization procedures. Data for 19 subjects were reported. Experimental group subjects received IM injections of allogeneic BMMNC (200 million in 15 ml) while control subjects received placebo infusions. All subjects were followed for at least 2 years, with blinding only up to the 6-month time point. No procedural-related adverse events were reported. Overall, 58 adverse events were reported, with 13 occurring in 6 experimental group subjects and 45 reported in 8 placebo group subjects. Of these, 25 were related to abnormalities in laboratory values, but the investigators did not attribute any of them to the BMMNC treatment. Another 14 events were related to complications of CLI. Significant increase in Ankle Brachial Pressure Index (ABPI) and ankle pressure were seen in the BMMNC group compared to the placebo group, with mean ABPI improvement of 0.214 and 0.004 respectively after 6 months (p=0.0018). The authors noted that no significant differences were seen between groups with regard to serum cytokine levels and blood lymphocyte profile, indicating that no T-cell proliferative response was elicited. The authors concluded that the use of allogeneic BMMNC is safe when injected via IM route at a dose of 2 million cells/kg body weight. They also state that improved ABPI and ankle pressure showed positive trend, warranting further studies.

There are several RCTs available addressing the use of autologous stem cell therapy to treat PVD. The first reported study included only 22 subjects with bilateral leg ischemia due to undisclosed etiology (Tateishi-Yuyama, 2002). For each subject, one leg was randomly selected to receive IM transplantation with BMMNC, the other was treated with IM PBMNC. At 24 weeks, legs injected with BMMNC were significantly improved compared to PBMNC with respect to ankle-brachial index (ABI) ($p<0.0001$), transcutaneous oxygen pressure (TcO2, $p<0.0001$), pain at rest (p=0.025), and pain-free walking (p=0.0001). The next study included 28 subjects with CLI due to advanced Type 2 diabetes (Huang, 2005). Study subjects were randomized to receive either stem cell therapy with PBMNCs administered via IM injection or IV prostaglandin therapy. The authors reported that there was significant improvement (p=0.05) in the stem cell group compared to the control group in terms of lower limb pain, ulcer healing, lower limb perfusion, ankle brachial index, and angiographic scores. The number of CLI-related amputations were also significantly better in the stem cell group (1 vs. 5, p=0.007). However, the study was not blinded, there was no placebo or sham intervention arm, and the study sample was very small. It is unclear whether the differences reported are attributable to the treatments given or other factors. Huang and colleagues (Huang, 2007) published an additional study that involved 150 subjects with TAO randomized to receive stem cell therapy with either PBMNCs or with BMMNCs via IM injection. Ankle-brachial index, skin temperature and pain at rest were all better in the PBMNC group. These findings contradict those reported by Tateishi-Yuyama, as discussed above (2002). An RCT conducted by Van Tongeren and others included 27 subjects with CLI of the legs due to undisclosed etiology (2008). Subjects were randomly assigned to receive BMMNC via either IM or a combination of IM/IA injections. At 12 months, 2 IM/IA group subjects had amputations vs. 7 in the IM only group. In the

remaining participants, regardless of group, treatment resulted in significant improvements in pain-free walking distance, overall pain, and ABI.

Fadini and others published the results of a meta-analysis of previously published studies (2010). This analysis looked at the results of autologous stem cell therapy for PVD with regard to the endpoints of change in ABI, TcO2, pain-free walking time, ulcer healing and amputations. Significant improvements were reported for all the measures when all studies were analyzed. When only controlled studies were considered, no significant differences were found for ABI and TcO2. Outcomes were evaluated between subjects with ASO vs. TSO. For subjects with TAO compared to those with ASO, significant benefits were noted for changes in ABI (p=0.021), TcO2 (p=0.03), pain scale (p=0.003), and pain-free walking distance (p=0.019). When looking at the data comparing PBMNCs vs. BMMNCs, PBMNCs were significantly better at improving resting pain (p=0.006) and BMMNCs were better with regard to ulcer healing times (p=0.038). No other significant differences were noted. The route of administration was also evaluated, comparing IM vs. IM/IA. The authors reported that ABI and TcO2 were significantly improved in subjects receiving IM but not IM/IA administration. With the exception of ulcer healing time, all other measures demonstrated equal benefit between groups. There was insufficient data to evaluate ulcer healing times. The authors note that most studies evaluated were not properly designed to report on safety-related issues and systematic reporting of adverse events was rare.

A small RCT was published by Szabo and colleagues in 2013. The study involved 19 subjects with late-stage no-option PVD randomly assigned to undergo either standard of care or treatment with VesCell™ autologous stem cell therapy. Follow-up assessments were conducted at 1 and 3 months, and at 2 years. No adverse events were attributed to the treatment methods during the study. However, 80% of the control subjects and 50% of the VesCell group subjects experienced adverse events. At 3 months, the difference in limb loss between the two groups was statistically significant (p=0.01). At 2 years, major amputation-free proportion was 70% in treated group and 40% in control group. At 3 months, the average change in ABI was -0.01 in the control group, and +0.36 ± 0.11 (p=0.01). At 2 years, the average change from baseline was 0.62 ± 0.07, (p=0.001). TcO2 was significantly improved in the VesCell group only at the 3 month time point (6.06 ± 4.0 in the VesCell group vs. -3.5 ± 5.4 in the control group; p=0.03). These results are interesting, but the small sample size limits the utility of these findings.

The results of another randomized, double-blind, placebo controlled trial involving 160 subjects with CLI receiving autologous BMMNCs (n=81) vs. sham treatment (n=79) was published in 2015 (The JUVENTAS Trial, Teraa, 2015). In this study, all subjects completed the 6-month time point, and 79% (127/160) completed the planned 12-month study. No differences were reported between groups with regard to the primary outcome, with amputation rates of 19% and 13% in the BMMNC group and control group, respectively (p=0.31). Additionally, no significant differences were noted between groups with regard to the combined safety outcome (15% vs. 19%, relative risk [RR]=1.46), all-cause mortality (5% vs. 6%, RR=0.78), or combined risk for amputation or death (23% vs. 16%, RR=1.43). The authors concluded, "Repetitive inter-arterial infusion of autologous BMMNCs into the common femoral artery did not reduce major amputation rates in subjects with severe, non-revascularizable limb ischemia compared to placebo."

A prospective observational case series study of 40 subjects with either systemic sclerosis (n=11) or ASO (n=29) who underwent implantation with autologous BMMNCs was reported (Takagi, 2014). The authors reported that there was a case of amputation in each group within 4 weeks after therapy. At 3 months, TcO2 significantly improved in subjects with systemic sclerosis (lcSSc, p<0.01) and those with ASO (p<0.05). At the 2 year follow-

up, the limb amputation rate was 9.1% in the lcSSc group and 20.7% in the ASO group (p=0.36), and the recurrence rate was 18.2% in the lcSSc group and 17.2% in the ASO group (p=0.95). The authors concluded that "bone marrow mononuclear cell implantation is safe and effective for intractable digital ulcers in lcSSc and ASO and is a promising therapeutic option for peripheral digital ulcer patients." However, this conclusion is significantly weakened when considering the methodological weaknesses of this small, open-label, nonrandomized study.

The most recent recommendations from the American Heart Association and the American College of Cardiology on the management of patients with lower extremity peripheral artery disease do not have any reference to the use of stem cell therapy for PVD (Bailey, 2019; Gerhard-Herman, 2017).

While the existing evidence to-date shows some potential benefit of autologous stem cell therapy for PVD, this evidence is from predominately small, uncontrolled, non-blind, nonrandomized studies. Furthermore, the data from available RCTs is somewhat contradictory. There are significant outstanding questions regarding optimal selection criteria for treatment candidate and cell type, method of administration, and whether or not similar benefits can be derived with the treatment of lower and upper extremities. Further investigation in the form of well-done, large scale, randomized controlled trials is needed to answer these questions and provide guidance for the use of stem cell therapy for PVD in the clinical setting.

Other Adult Stem Cell Therapies

The study of other adult stem cell types for stem cell therapy has been limited, with most studies using animal models. Scientists have discovered neuronal stem cells from the brain and spinal cord, and small studies are underway to test olfactory ensheathing glial cells for regenerating spinal cord tissue. Human teratocarcinoma cell line (hNT) cells have shown promise in animal models for treating ALS and stroke. Muscle-derived stem cells are being investigated in rat models for incontinence and cardiac damage. Other possible adult stem cells under investigation include liver stem cells, pancreatic stem cells, corneal limbal stem cells, and mammary stem cells. Stem cells are also being investigated from the salivary glands, skin, and heart. Although small clinical trials are underway, a great deal of research is needed to assess the safety and efficacy of adult stem cell therapies (NIH, 2018).

Exosome Therapy

Some clinics offer products marketed as containing exosomes (membrane bound extracellular vesicles produced by the endosomes of cells). The treatments are purportedly produced from stem cells, often placental derived mesenchymal stem cells. At this time, there are no FDA-approved exosome products, and no credible safety and efficacy data evaluating these marketed treatments. The FDA has issued a public safety notification on the risks of exosome products (FDA, 2019).

Autologous Cell Therapy for Treatment of Damaged Myocardium and Other Applications.

The use of various cell types, such as hematopoietic stem cells, BMMC, skeletal myoblasts, mesenchymal stem cells (MSC), and circulating or bone marrow-derived EPCs are currently being evaluated in clinical trials utilizing various delivery techniques to revascularize or remodel injured myocardial (heart) tissue. The optimal cell type that can develop into functioning cardiac muscle has yet to be identified. There is also uncertainty regarding the timing

of the transplantation post-infarct and the cell delivery mode (directly into myocardium, intracoronary artery or sinus, or intravenously). Additionally, there are concerns related to harvesting autologous cells safely during the immediate post-infarct period. Skeletal myoblasts may offer a unique advantage because they are easy to access through a muscle biopsy. However, the harvested tissue must undergo culture to expand the number of skeletal myoblasts. In some trials, biopsy to obtain skeletal myoblasts must occur 3 to 6 weeks before the anticipated implantation of the cultured cells.

At this time, no autologous cell therapy (ACT) technologies specific to the treatment of damaged myocardium have received United States (U.S.) Food and Drug Administration (FDA) approval. While FDA approval is not required for autologous cells processed on site with established laboratory procedures and injected with existing catheter devices, specialized technologies do require FDA approval. The 21st Century Cures Act (2016) established new expedited product development programs, including the regenerative medicine advanced therapy (RMAT) designation.

According to the FDA, a drug is eligible for the RMAT designation if:

- The drug is a regenerative medicine therapy (that is, cell therapy), therapeutic tissue engineering product, human cell and tissue product, or any combination product; AND
- The drug is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; AND
- Preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition (FDA, 2021).

There are several products under investigation for the treatment of damaged myocardium. MyoCell® (U.S. Stem Cell, Inc., Sunrise, FL) consists of autologous skeletal myoblasts that are expanded and supplied as a cell suspension for injection into the damaged myocardial area. According to the manufacturer, phase II and III trials of MyoCell are underway. Notably, in 2017 the manufacturer terminated its RMAT application for the MyoCell product. Additional progenitor cell products are being commercially developed, including the Ixmyelocel-T (Vericel Corp., Cambridge, MA), MultiStem® (Athersys Inc., Cleveland, OH) and the CardiAMP™ (BioCardia® Inc., San Carlos, CA). In 2017, the manufacturer of the Ixmyelocel-T product obtained the RMAT designation for treatment of advanced heart failure (HF) due to ischemic dilated cardiomyopathy (DCM). This autologous product is produced from the individual's own bone marrow by selectively expanding bone marrow mononuclear cells. The MultiStem is an allogeneic bone marrow-derived adult stem cell product and, as such, is not addressed in this document. The CardiAMP Cell Therapy system includes a proprietary cell processing system, to isolate, process and concentrate autologous stem cells from the bone marrow and a proprietary delivery system to percutaneously inject the cells directly into the myocardium. The manufacturer of the CardiAMP system has obtained an investigational device exemption (IDE) from the FDA for investigational use only.

Specialized catheters to inject cells directly into the heart tissue, (such as the MyoCath™ [Bioheart, Inc., Ft. Lauderdale, FL]), are also under investigation for FDA approval. Bioheart, Inc. is currently conducting clinical trials, as part of the FDA approval process. The trials are evaluating individuals with a previous myocardial infarction (MI) who undergo epicardial implantation of the cultured myoblasts at the time of coronary artery bypass grafting and individuals with a prior MI and subsequent HF, who undergo subendocardial implantation using the MyoCath device during a catheterization procedure. All participants must receive an implantable cardiac

defibrillator (ICD), based on preliminary data suggesting that the implanted myoblasts may be arrhythmogenic (cause irregular heartbeats).

The existing evidence on the use of stem cells to treat chronic ischemic heart disease, HF and acute myocardial infarction (AMI) was evaluated in two Cochrane reviews. In the review of chronic ischemic heart disease and HF, there is low quality evidence that stem cell treatment improves left ventricular ejection fraction (LVEF) or reduces mortality in the short term, or that therapy reduces the incidence of non-fatal MI or improves New York Heart Association (NYHA) functional status in the long term (Fisher, 2016). In AMI, a total of 41 randomized controlled trials (RCTs) with 2732 individuals were included in the review. The authors noted there was no clinically relevant improvement in morbidity, quality of life/performance or LVEF reported with ACT over controls. The authors summarized that the evidence was insufficient to allow for any conclusions to be drawn and that further adequately powered trials are needed (Fisher, 2015).

Heldman (2014) conducted an RCT (phase I and II) to evaluate the safety of transendocardial stem cell injection with autologous MSCs and bone marrow mononuclear cells (BMCs) in 65 individuals with ischemic cardiomyopathy (CM) and LVEF of less than 50%. Study investigators compared MSCs (n=19) with the placebo group (n=11), and BMCs (n=19) with the placebo group (n=10). Participants were followed for a period of 1 year. No participants experienced treatment-associated serious adverse events when evaluated at 30 days. At 1 year, the rate of adverse events was 31.6% (95% confidence interval [CI]; 12.6% to 56.6%) for MSCs, 31.6% (95% CI; 12.6%-56.6%) for BMCs, and 38.1% (95% CI; 18.1%-61.6%) for placebo. At 1 year follow-up, the Minnesota Living With Heart Failure scores significantly improved in individuals treated with MSCs (-6.3; 95% CI; -15.0 to 2.4; p=0.02) and with BMCs (-8.2; 95% CI; -17.4 to 0.97; p=0.005), but not in individuals in the placebo group (0.4; 95% CI; -9.45 to 10.25; p=0.38). Additionally, the 6-minute walk distance increased with MSCs only (p=0.03). No changes were observed in left ventricular chamber volume and LVEF. Results suggested that transendocardial stem cell injection with MSCs or BMCs appeared to have a relatively good safety profile in individuals with chronic ischemic CM and left ventricular (LV) dysfunction. Study authors emphasized that the study was hampered by several limitations including small sample size, and no definitive conclusions regarding the safety and clinical effects can be made. Larger, well-designed studies are necessary to further assess the safety and efficacy of this therapeutic approach.

Lee (2014) conducted a pilot RCT to evaluate the safety and efficacy of adult MSC treatment following AMI. Participants were randomized to the group treated with autologous BM-derived MSCs at 1 month (n=33) or the control group (n=36). The primary endpoint was any change in LVEF assessed at 6 months. Individuals in the BM-derived MSC treatment group experienced significant improvement in the LVEF at 6 months compared with the control group (p=0.037). There was no incidence of toxicity during intracoronary administration of MSCs, and no significant adverse cardiovascular events were observed during follow-up. Study authors concluded that intracoronary infusion of human BM-derived MSCs at 1 month was relatively safe, well-tolerated, and resulted in fair improvement in LVEF, when assessed at 6 months of follow-up.

Assmus and colleagues (2002) reported on the results of the Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI) study. This study included 20 individuals who had already undergone revascularization after an AMI and received either BMCs or circulating blood-derived progenitor cells infused into the infarct artery during a second catheterization procedure. Cardiac function was evaluated before and after the transplantation procedure. After 4 months, the authors reported an improvement in

LVEF, regional wall motion, and LV end diastolic volume (LVEDV). Subjects in this same study were evaluated in a subsequent analysis to identify predictors of clinical outcomes after AMI following treatment with BMCs or circulating blood-derived progenitor cells (Assmus, 2014). Subjects were followed for a mean period of 58 months. Seven subjects in the BMC group versus 15 subjects in the placebo group died (p=0.08) and 5 BMC subjects versus 9 placebo subjects required rehospitalization for in-stent restenosis of the infarct vessel (p=0.023). Univariate analysis demonstrated that the predictors of adverse events in the placebo group were age, the CADILLAC risk score, treatment with aldosterone antagonists and diuretics, changes in LVEF, LV end-systolic volume (LVESV), and N-terminal pro-Brain Natriuretic Peptide (p=0.01 for all) at 4 months in all subjects, as well as the placebo group. However, in the treatment group, only two outcomes were associated with significant improvements.

Mathiasen (2013) evaluated the long-term safety and efficacy of intramyocardial injection of autologous bone-marrow derived mesenchymal stromal cells (BMMSCs) in individuals with severe but stable coronary artery disease (CAD) and refractory angina (n=31) over a follow-up period of 3 years. Subjects had no additional revascularization options available to them. Investigators injected BMMSCs into an ischemic region of the heart. Study results demonstrated statistically significant improvements in total exercise time (p=0.0016), angina class (p<0.0001), the weekly occurrence of angina attacks (p<0.0001), and treatment with nitroglycerine (p=0.0017). In terms of the Seattle Angina Questionnaire, participants experienced significant improvements in several measures, including the physical limitation score, angina stability score, angina frequency score, and quality of life (QOL) score (p<0.0001 for each measure). Results also demonstrated significantly reduced hospital admissions for the following conditions: stable angina (p<0.0001), revascularization (p=0.003) and overall cardiovascular disease (p<0.0001).

Results from the C-CURE (Cardiopoietic stem Cell therapy in heart failURE) prospective, multi-center, blinded, RCT were reported by Bartunek and colleagues (2013). The primary endpoint of the study was feasibility and safety of autologous BM-derived cardiopoietic stem cell therapy at 2 years follow-up. A total of 319 individuals with chronic ischemic HF were screened at 9 centers, and 47 individuals were randomized to receive standard of care or standard of care plus BM-derived cardiopoietic stem cell therapy. In the cell therapy arm, bone marrow was harvested and MSCs were isolated and expanded by exposure to cardiogenic cocktail treatments. The cardiopoietic MSCs were injected endoventricularly with guidance from electromechanical mapping of the participants' hearts. Cardiopoietic stem cell expansion successfully met pre-determined criteria for 75% (n=21 individuals) and successful delivery occurred for all cases transplanted. There was no evidence of increased cardiac or systemic toxicity induced by cardiopoietic MSC therapy. The LVEF at 6 months was improved for the cardiopoietic MSC treatment group with a 7% increase from 27.5% (95% CI; 25.5% to 29.5%) at baseline to 34.5% (95% CI; 32.5% to 36.6%) (n=21, p<0.0001). LVEF was unchanged in the control group (n=15) from baseline 27.8% (95% CI; 25.8% to 29.8%) to 28.0% (95% CI; 26.1% to 30.6%) at 6 months. Other indicators, including the 6-minute walk test and composite scores such as QOL, cardiac function, and clinical endpoints improved with cell therapy, compared with standard of care. The study authors concluded the trial was not powered as a therapeutic efficacy trial. A full 30% of the participants, for whom adequate cells could not be obtained, were dropped from the analysis. Comparative effectiveness trials will be required to determine if cardiopoietic MSC therapy is an effective regenerative strategy for management of HF.

Duckers and colleagues (2011) reported results from the SEISMIC study, a phase IIa RCT of percutaneous myoblasts placed, along with ICD, in individuals with HF. A total of 26 individuals were randomized to the treatment group that involved ICD and myoblasts, and 14 participants were randomized to the control group that

involved optimal medical treatment. The trial was designed to examine the safety and feasibility of the MyoCell transplantation procedure. There was no significant difference in the global LVEF at 6 months follow-up. There were no significant differences between the treatment and control groups with regard to the NYHA classification and 6-minute walk test results. The study authors concluded the data demonstrated the feasibility of myoblast implantation, but the results were not superior to standard optimal medical treatment and ICD placement.

LateTIME, a phase II randomized, double-blind, placebo-controlled trial, investigated the impact of intracoronary infusion of autologous BMC in individuals with LVEF less than or equal to 45% after percutaneous stent placement (Traverse, 2011). A group of 87 participants were randomized to BMC infusion or placebo. BMC treatment was provided 2 to 3 weeks after the initial MI and primary study endpoints were improvement in global and regional LV function. The mean LVEF change from baseline to 6 months was not different in the BMC treatment group (48.7% to 49.2%), compared with the placebo group (45.3% to 48.8%). The authors concluded that delivery of BMC 2 to 3 weeks following MI is not effective.

In a companion trial to the LateTIME, the TIME trial prospectively evaluated the effect of BMC therapy during the first week after stenting with primary percutaneous coronary intervention (PCI). The double-blind, placebo-controlled trial randomized 120 participants (LVEF ≤ 45% after PCI) to BMC therapy at day 3 or day 7 (Traverse, 2012). All participants had autologous BMCs isolated after undergoing bone marrow aspiration. A second randomization assigned individuals to receive 150 x 106 total nucleated cells (70-80% of BMCs) or to placebo. Infusions of BMCs or placebo were administered in the infarct-related artery within 12 hours of aspiration. Change from baseline and at 6 months in global LVEF and regional LV function measured by MRI, were the primary endpoints. At 6 months, there was no significant BMC treatment versus placebo effect demonstrated by improved LVEF.

Similarly, the FOCUS-CCTRN (First Mononuclear Cells injected in the United States conducted by the CCTRN [Cardiovascular Cell Therapy Research Network]), a phase II randomized, double-blind, placebo-controlled trial investigated the safety and efficacy of transendocardial-delivered BMCs in participants with chronic ischemic heart disease and LV dysfunction with HF and/or angina (Perin, 2012). The primary endpoints evaluated at 6 months included changes to the LVESV on echocardiography, maximal oxygen consumption, and reversibility on single photon emission tomography (SPECT). There were no statistically significant differences between BMC versus placebo for all of the primary endpoints (Perin, 2012).

A meta-analysis by Gyöngyösi and colleagues (2015) studied the individual data of 1252 participants from 12 RCTs involving intracoronary cell therapy after AMI. The overall results of the analysis of the primary endpoint, freedom from major adverse cardiac and cerebrovascular events (MACCE), was found to be highly consistent, in direction and magnitude, with the results of the within-trial analysis. The results showed there was no significant difference between the MACCE rates of those who received cell therapy versus those in the control groups (14.0% versus 16.3%; hazard ratio [HR], 0.86; 95% CI; 0.63–1.18; p=0.884). In addition, there were no significant differences in the death rate, LVEF, LVEDV or LVESV between the groups. Previous meta-analyses have reported inconsistent results; some meta-analyses reported a benefit in those receiving cell therapy while other meta-analyses did not report a benefit. The authors noted that, while previous meta-analyses used information from published articles resulting in data heterogeneity, this study used individual participant data in their analysis.

San Roman and colleagues (2015) conducted a four-arm multicenter, prospective, randomized, open-labeled trial comparing the efficacy of BMMC (n=30), G-CSF mobilization (n=30) and both therapies (n=29) to standard therapy (n=31) in AMI. Following infarct-related artery revascularization, individuals received treatment based on the regimen assigned to each treatment group. The primary endpoint was the absolute change (baseline to 12 months) in global LVEF and in LVESV. At 12 months follow-up, there was no improvement in LVEF in any of the treatment arms, compared to the control, and MACE were not significantly different between the groups. The reported 4% overall improvement in LVEF was comparable to improvements reported in contemporary randomized reperfusion trials with a similar testing population.

ACT is in the early stages of development in evaluating of use for treatment of orthopedic, vascular and rheumatologic applications. At this time, there is not sufficient evidence in the peer-reviewed medical literature, in terms of the safety and efficacy, to support the use of ACT for these investigational indications. Further research with randomized controlled trials is needed to verify the benefit and safety of ACT for all uses.

Autologous Blood-derived Products

At this time, there are very few published peer-reviewed articles addressing the use of autologous blood-derived wound products, (e.g., Aurix). The only available controlled trial addressing these products was published by Gude in 2019. This pragmatic randomized controlled trial investigated the treatment of 12 diabetic foot ulcers using Aurix hematogel plus standard care (n=66) vs. standard care alone (n=63) for up to 12 weeks using a Medicare Coverage with Evidence Development paradigm. The original protocol called for enrollment of 760 subjects, but this plan was discarded due to recruitment problems. The authors reported a significant benefit from the use of Aurix vs. control treatment with regard to time-to-heal advantage, with 48.5% of wounds healing with Aurix vs. 30.2% in the control group (log-rank p=0.0476). Additionally, a higher percentage of healing was observed for Aurix across all wound severities (Wagner grade 1-4). A subgroup analysis revealed a significant healing advantage for Aurix when treating wounds accompanied by peripheral arterial disease (p=0.0319).

While these results are promising, additional data is needed to establish the safety and efficacy of autologous blood-derived wound products, and to identify what patient populations may have derive benefit from such treatment.

Platelet Rich Plasma

Platelet rich plasma (PRP) has been available for several decades and its use has been proposed for a wide variety of medical conditions. The medical literature currently lists dozens of studies addressing the use of PRP for a wide variety of indications including chronic skin wounds, maxillofacial and sinus surgery, various musculoskeletal injuries and surgical procedures, endovascular surgery, plastic surgery, and thoracic and cardiac surgery. Unfortunately, most available studies are small, uncontrolled, retrospective, and/or have short follow-up periods, constituting significant methodological flaws, which limit the utility of the studies in evaluating the benefits of PRP use.

Chronic lateral epicondylitis (LE)

There are several RCTs published addressing the use of PRP to treat chronic lateral epicondylitis (LE), also known as tennis elbow. The largest RCT available to date involved 230 subjects with chronic LE randomized in a double-

blind fashion to receive PRP (n=116) or active controls who received needling only (n=114) (Mishra, 2013). After receiving a local anesthetic, all subjects had their extensor tendons needled with or without PRP. Subjects were followed for up to 24 weeks. No significant differences were noted between groups at 12 weeks (n=192, 83.5%). At 24 weeks (n=119, 51.8%), the PRP-treated subjects reported an improvement of 71.5% in their pain scores compared with 56.1% in the control group (p=0.019). Additionally, 29.1% of the PRP-treated group reported significant elbow tenderness versus 54.0% in the control group (p=0.009). Success rates for the subjects completing the 24-week follow-up period were 83.9% in the PRP group vs. 68.3% in the control group (p=0.037). No significant complications occurred in either group. The authors concluded that at 24 weeks clinically meaningful improvements were found in subjects treated with leukocyte-enriched PRP compared with an active control group. However, these results must be viewed with care, since the loss to follow-up was so large at 24 weeks (48.2%). Peerbooms and others (2010) published an RCT describing the use of PRP in 100 subjects with LE randomly assigned to receive a single injection of PRP (n=51) or corticosteroids (n=49). After 1 year, 25 of the 49 subjects (51%) in the corticosteroid group and 37 of the 51 (73%) in the PRP group were deemed "successful" with greater than 25% reduction in DASH Outcome Measure scores (p=0.005). The authors note that further study of the use of PRP is warranted. Krogh (2013) described a study that involved 60 subjects assigned to receive treatment with a single injection of either PRP, saline, or glucocorticoid. Pain reduction at 3 months was observed in all 3 groups, with no statistically significant difference between the groups (p=0.717). At 1 month, however, glucocorticoid reduced pain more effectively than did both saline and PRP. At 3 months, glucocorticoid was more effective than PRP and saline in reducing color Doppler activity (p=0.0001) and tendon thickness (p=0.002). The authors concluded that a single injection with either PRP or glucocorticoid was not significantly superior to a saline injection for reducing pain and disability over a 3-month period in individuals with LE. Two other RCTs compared PRP to autologous blood injection (ABI). A study by Creaney (2011) involved 150 subjects (n=80 PRP group, n=70 ABI Group). The follow-up for this study was 6 months, and the authors noted that at 6 months the success rate in the PRP group was 66% vs. 72% in the ABI group (p=not significant), and there was a higher rate of conversion to surgery in the ABI group (20%) versus the PRP group (10%). Montalvan (2016) described the results of a double-blind placebo-controlled RCT involving 50 subjects assigned to receive either conditioned plasma (n=25) or saline solution (n=25). Subjects were monitored at baseline and 1, 3, 6 and 12 months. The primary outcome was relative improvement from baseline to 6 months in pain score on visual analog scale. The secondary outcome was Roles-Maudsley score and the assessment of pain on isometric contraction of extensor carpi radialis brevis and extensor digitorum communis. Three subjects dropped out from each study group before the 6-month time period. In the PRP group, the pain score decreased significantly from a mean of 6.8 at baseline to 2.5 at 6 months and 1.6 at 12 months. In the saline group, the results changed from 7 at baseline to 2.1 and 1.8, respectively. At 6 months, no statistically significant difference was found between groups for relative improvement in pain score (p=0.24). The authors also reported no significant difference between groups with regard to secondary criteria. They concluded that PRP injections, for epicondylitis of recent evolution, were not more efficacious than saline injections. Thanasas (2011) reported on a smaller RCT involving 28 subjects assigned to receive a single injection of either autologous blood or PRP, with 14 subjects in each group. The results indicated that the visual analog pain scale was only significantly different at 6 months, in favor of the PRP group (p<0.5). No statistically significant differences were noted on the pain scale or the Liverpool elbow score. These studies present a mixed picture regarding the possible benefits to PRP therapy for LE.

A systematic review published in 2014 by de Vos and Weir evaluated the available literature on PRP treatment for epicondylar tendinopathy. The authors included six studies that met inclusion criteria, of which four were considered to be of high quality. Of these studies, three high-quality and two low-quality studies showed no

significant benefit at the final follow-up measurement or in predefined primary outcome score when compared with a control group. Only one high-quality study showed a beneficial effect of a PRP injection when compared with a corticosteroid injection (corticosteroid injections are harmful in tendinopathy). The conclusion of this analysis was that there is strong evidence that PRP injections are not efficacious in chronic LE.

Mi et al. (2017) reported the results of a meta-analysis including eight RCTs involving 511 subjects comparing PRP to steroids in reducing pain and improving function in the treatment of epicondylar tendinopathy. Their results demonstrated no significant differences between groups with regard to pain relief in the short-term (2 to 4 weeks, p=0.03 and 6 to 8, p=0.24) or in the intermediate-term (12 weeks, p=0.35). They did find significant benefits to steroid treatment vs. PRP for function in the short-term (2 to 4 weeks, p<0.001; 6 to 8 weeks, p<0.001). In contrast, their findings indicated that PRP was superior to steroids for pain relief in the long-term (half year, p<0.001; 1 year, p<0.001) and for functional improvement in the intermediate-term (12 weeks, p<0.001) and the long-term (half year, p<0.001; 1 year, p<0.001). They concluded, "PRP appears to be more effective in relieving pain and improving function in the intermediate-term (12 weeks) and long-term (half year and one year)."

In 2016, Tsikopoulos and colleagues published the results of a meta-analysis evaluating RCTs involving the use of PRP for tendinopathies vs. either placebo or dry needling. The primary condition treated was epicondylitis in two studies, rotator cuff tendinopathy in two studies, and patellar tendinopathy in the last. The authors identified five studies involving 190 subjects that met inclusion criteria. The buffy coat method of PRP preparation was used in 80% of the studies, and did not involve the use of activated platelets. There was a statistically significant difference in favor of PRP for pain intensity at 2 or 3, and 6 months after intervention (p=0.01) and for functional disability at 3 months after treatment (p=0.01).

A new PRP-containing product, Vergenix Soft Tissue Repair (STR) Matrix, was evaluated in a case series study of 40 subjects with LE (Farkash, 2018). STR is an injectable gel composed of cross-linked bioengineered recombinant human type I collagen combined with autologous platelet-rich plasma. The authors reported a 59% reduction at 6 months in the mean Patient-Rated Tennis Elbow Evaluation (PRTEE) score (p<0.001). Results in the 12-Item Short-Form Health Survey questionnaire (SF-12) demonstrated improvement from a mean score of 30.7 to 37.7 at 6 months. Grip strength increased from 28.8 kg at baseline to 36.8 kg at 6 months. The lack of a control group and other methodological weaknesses impair the reliability and generalizability of these results.

Shoulder conditions

The use of PRP for arthroscopic repair of the shoulder has been addressed in several moderately sized RCTs (Carr, 2015; Castricini, 2011; Gumina, 2012; Rodeo, 2012; Ruiz-Moneo, 2013; Walsh, 2018; Weber, 2013). Of these studies, three were double-blind studies (Carr, Ruiz-Moneo, and Weber). All of these trials found no significant benefit to the use of PRP with regard to perioperative morbidity, clinical outcomes, or structural integrity. A meta-analysis conducted by Zhao and colleagues in 2015 involved these studies, except the study by Carr, in addition to several smaller RCTs. Their findings showed that the available evidence does not support the use of PRP for full-thickness rotator cuff repair, and that the majority of studies reported no significant benefit to the addition of PRP to standard surgical repair.

A study by Battaglia (2014) investigated the difference in outcomes between PRP and hyaluronic acid (HA) for the treatment of hip osteoarthritis. This study involved 100 subjects evenly distributed between groups. The authors

state that at no time point (1, 3, 6, 12, or 24 months) were significant differences noted between groups with regard to Harris Hip Score or visual analog pain scale ratings. They concluded that PRP was not superior to HA for the treatment of osteoarthritis (OA) of the hip. Another study by Dallari (2016) reported the results of an RCT involving 111 subjects with hip osteoarthritis assigned to treatment with 3 weekly injections of either PRP (n=44), PRP+HA (n=31), or HA alone (n=36). Subjects were followed for 12 months post treatment with no withdrawals or loss to follow-up. At all time points, the PRP group had the lowest VAS pain scores. The authors pointed out that at the 6-month follow-up in particular, the mean VAS score was 21 in the PRP group, 35 in the PRP+HA group, and 44 in the HA group ($p<0.0005$ for PRP vs. HA and $p=0.007$ for PRP vs PRP+HA). The McMaster Universities Osteoarthritis Index (WOMAC) score of the PRP group was significantly better at 2 month and 6 month follow-up vs. the other groups, but not at the 12-month follow-up (at 2 months: $p<0.009$ for PRP vs. HA and $p=0.026$ for PRP vs PRP+HA; at 6 months: $p<0.009$ for PRP vs. HA and $p=0.0005$ for PRP vs PRP+HA; at 12 months: $p<0.005$ for PRP vs. HA and $p=0.007$ for PRP vs PRP+HA). Positive response at 12 months was reported for participants in all groups with regard to WOMAC scores ($p=0.04$), but not with VAS or Harris Hip scores (p=NS).

Anterior cruciate ligament (ACL) reconstruction surgery

Two RCTs have investigated the use of PRP for the prevention of tunnel widening following anterior cruciate ligament (ACL) reconstruction surgery (Mirzatolooei, 2013; Vadalà, 2013). These small studies (n=50 and 40, respectively) both reported no significant benefit to the use of PRP to prevent tunnel widening. It is unclear if further studies into this use of PRP would provide data demonstrating any benefit to PRP for this indication.

Seijas (2013) reported the results of an RCT involving 98 subjects evaluating the use of PRP in tendon graft remodeling following ACL reconstruction. The findings, based on MRI studies, indicated that PRP had a significant impact on remodeling, with more subjects in the PRP group vs. controls attaining higher stages of remodeling at 4 months ($p=0.003$), 6 months ($p=0.0001$), and 12 months ($p=0.354$). However, no clinical data is presented, and it is not clear if the level of improved tendon remodeling reported provides any significant clinical outcome benefits. Further investigation is warranted. Another RCT, conducted by Nin et al (2009) involved 100 subjects, 50 receiving standard surgical treatment and 50 undergoing ACL reconstruction with the addition of PRP. There were no significant differences between groups reported with regard to MRI appearance of the graft, inflammatory markers, clinical evaluation scores (visual analog scale, International Knee Documentation Committee), or KT-1000 arthrometer testing. Finally, Vogrin (2010) reported the results of a single-blinded RCT involving 50 subjects receiving similar group placement as used in the Nin study (25 in each group). The authors reported finding a significantly higher level of vascularization in the osteoligamentous interface vs. control group ($p<0.001$), but no evidence of revascularization in the intra-articular part of the graft. Further investigation into this treatment method is warranted.

Total knee arthroplasty

An RCT investigating the use of PRP for the treatment of postoperative pain and blood loss following total knee arthroplasty was done by Aggarwal and others (2014). This study randomized 40 subjects (59 knees) who were randomized to receive treatment with PRP (n=17, 27 knees) or without PRP (n=23, 32 knees). In the immediate postoperative period, the PRP group had a significantly lower reduction in hemoglobin and need for blood transfusion ($p=0.00$ and $p=0.001$, respectively), experienced less pain ($p=0.00$), and required fewer narcotics than the control group ($p=0.00$). At 3 months there was a significant difference in range of motion ($p=0.01$), no

significant difference in wound scores (p=0.311), and a significant difference in Knee Society Score (KSS) and WOMAC scores at 12 weeks (p=0.00, p=0.00 respectively). No significant difference was found at 6 months. These findings warrant further investigation.

A meta-analysis of studies investigating the use of PRP vs. placebo following TKA procedures published by Li (2017) involved 11 trials and 1316 subjects. The pooled results indicated that PRP significantly increased range of motion (ROM) on the third day (p=0.000) and at 3 months postoperatively (p=0.000). However no statistical differences between groups were noted in WOMAC questionnaire scores at 3 months (p=0.190), pain intensity at 24 hours, 48 hours or 7 days (p=0.77, p=0.76, and p=0.99, respectively), or infection rates (RR=0.64, p=0.464).

Osteoarthritis of the knee and ankle

PRP for the treatment of osteoarthritis of the knee (OA) has been the subject of several RCTs. The largest of these studies involved 176 subjects treated with either PRP or with hyaluronic acid (HA) (Sánchez, 2012). Response was judged based upon 50% decrease in knee pain from baseline to 24 weeks. The authors reported that the rate of response to PRP was 14.1% higher than that seen in the HA group (p=0.044). However, there were no significant differences between groups reported on the pain, stiffness, and physical function scales on the Western Ontario and WOMAC. The next largest RCT involved 120 subjects assigned to undergo unblinded treatment with either PRP (n=60) or with HA (n=60) (Cerza, 2012). At week 4, both groups showed a significant reduction in overall WOMAC score compared with baseline. The difference recorded between the PRP and the HA group was statistically significant (p<0.001) at this time point, with PRP providing significant improvement vs. HA. At weeks 12 and 24, continuous improvement in the subjects treated with PRP was noted, and a slight worsening was reported in subjects treated with HA (p<0.001). Both groups were still significantly better at week 24 compared to baseline. Another RCT, a double-blind study, included 78 subjects randomized to receive one of three treatments: Group A received a single injection of PRP (n=52 knees), Group B received two injections of PRP 3 weeks apart (n=50 knees), and Group C received a single injection of normal saline (n=46 knees) (Patel, 2013). Statistically significant improvement in all WOMAC parameters was noted in groups A and B within 2 to 3 weeks, lasting until the final follow-up at 6 months. A slight, but statistically insignificant, worsening was reported at the 6-month follow-up. The three groups were compared with each other and no improvement was noted in group C as compared with the other two groups (p<0001). No differences were noted between groups A and B, indicating that a single injection of PRP was sufficient to provide benefit. A third non-blinded RCT involved 120 OA subjects assigned to undergo treatment with either PRP (n=60) or HA (n=60). Both the PRP and HA groups demonstrated statistically significant improvement in both clinical evaluation schemes of the WOMAC at the 3- and 6-month follow-up periods with respect to baseline. The PRP group was reported to have had significantly better WOMAC scores at both the 3- and 6-month follow-up times (p<0.01 for both). A small RCT involving 30 subjects with osteoarthritis of the knee was published by Smith (2016). Subjects were assigned treatment with either autologous conditioned plasma or placebo (n=15 each group). The WOMAC scores in the plasma group at 1 week were significantly decreased compared with baseline scores, and the scores for this group remained significantly lower throughout the study duration. At 12 months post-treatment, subjects in the plasma group were reported to have improved their overall WOMAC scores by 78% from their baseline score vs. 7% in the placebo group.

A meta-analysis of 14 studies involving 1423 subjects receiving PRP for treatment of knee osteoarthritis (OA) was published by Shen (2017). The use of controls was reported to be homogeneous, involving saline placebo, HA, ozone, and corticosteroids. They reported that the risk of bias assessment showed that 4 studies were considered as

moderate risk of bias and 10 as high risk of bias. The findings reported that compared with controls, PRP significantly reduced WOMAC pain subscores at 3, 6, and 12 months follow-up (p=0.02, p=0.004, and p<0.001, respectively), improved WOMAC physical function subscores at 3, 6, and 12 months (p=0.002, p=0.01 and p<0.001, respectively), improved total WOMAC scores at 3, 6 and 12 months (all p<0.001). PRP was not found to increase the risk of post-injection adverse events (RR=1.40, p=0.24).

These studies point to promising benefits of PRP therapy for individuals with OA. However, evidence from larger double blind RCTs is needed to properly evaluate this treatment method.

In 2021, the American Academy of Orthopaedic Surgeons (AAOS) released a guideline addressing management of osteoarthritis of the knee (non-arthroplasty). This document addressed the use of PRP, and the committee concluded that:

> Further research in this area should embrace detailed osteoarthritis characterization including sub-group analyses and osteoarthrosis severity stratification. Furthermore, using clinically relevant outcomes and controls for bias are warranted along with cost-effectiveness analysis. Specifically, to platelet rich plasma it will be of upmost importance to include comprehensive platelet rich plasma characterization and description of platelet rich plasma preparation protocol.

In 2020, the AAOS released an evidence-based clinical practice guideline for the management of glenohumeral joint osteoarthritis. The workgroup included recommendations for the use of PRP concluding that: "in the absence of reliable evidence, it is the opinion of the work group that injectable biologics, such as stem cells or platelet-rich plasma, cannot be recommended in the treatment of glenohumeral osteoarthritis. *Strength of Recommendation: Consensus*"

In 2021, Paget and colleagues reported finding from the Platelet Rich plasma Injection Management for Ankle osteoarthritis study (PRIMA), a randomized, double-blinded trial in The Netherlands. Individuals were randomized (1:1) to receive either two ultrasonography-guided intra-articular injections of PRP (n=45) or placebo (saline; n=52). Participants were excluded for concomitant osteoarthritis of other joints of the lower extremities or for undergoing an ankle surgery in the past 12 months. At 6 months, the mean American Orthopaedic Foot and Ankle Society (AOFAS) score improved by 10 points (from 63 to 73 points [95% CI, 6-14]; P<0.001) in the PRP group and 11 points (from 64 to 75 points [95% CI, 7-15]; P<0.001) in the placebo group. In the PRP group there were 13 adverse events reported and eight in the placebo group. The authors concluded that the results "do not support the use of PRP injections for ankle osteoarthritis."

Sternal wound infections

The treatment of sternal wound infections (SWI) with PRP has been described in a small number of studies. A large RCT involving 196 subjects who underwent cardiopulmonary bypass at risk of deep SWI (DSWI) were assigned to either application of autologous PRP before sternal wiring (n=97) or no PRP (n=99) (Dörge, 2013). The authors reported no significant differences between groups with regard to the incidence of DSWI (6.2% vs. 3.0%, p=NS). Serraino (2015) reported on the results of an RCT involving 1093 subjects who underwent cardiac surgery through median sternotomy. Subjects were assigned to receive care either with or without PRP applied inside the sternotomy wound prior to closure. The authors reported that the incidence of DSWI was significantly higher in the

control group vs. the PRP group (1.5% vs. 0.20%, p=0.043). Superficial sternal wound infections (SSWIs) were reported to also have been significantly higher in the control group vs. the PRP group (2.8% vs. 0.5%, p=0.006).

Other Conditions

PRP has been investigated for the treatment of a large number of other conditions, including aortic arch repair (Zhou, 2015), burn wounds (Brown, 2016), carpal tunnel (Raeissdat, 2018; Wu, 2018), chronic skin wounds (de Leon, 2011; Frykberg, 2010; Guthrie, 2016; Moneib, 2017; Sakata, 2012), degenerative disk disease (Tuakli-Wosornu, 2016), diaphyseal fractures (Singh, 2017), distal radius fracture (Namazi, 2016), erectile dysfunction (AUA, 2020; Poulios, 2021; SMSNA, 2021), frozen shoulder (Lin, 2018), lasik eye surgery (Javaloy, 2013), long bone non-unions (Calori, 2008; Mariconda, 2008), pilonidal sinus repair (Mostafaei, 2018), plantar fasciitis (Jain, 2018; Johnson-Lynn, 2018; Mahindra, 2016), postoperative chylothorax patching (Alamdari, 2018), refractory thin endometrium (Kim, 2019), rotator cuff calcification (Verhaegen, 2016), temporomandibular disorders (Nitecka-Buchta, 2019), total knee replacement (TKR) surgery (Berghoff, 2006; Everts, 2007; Gardner, 2007), and others. As stated above, these studies have small sample sizes and other serious design flaws that prevent the conclusions from being more widely generalized to clinical practice. Additionally, many of these studies concluded that there is little, if any, benefit to the use of PRP. One exception to this is the use of PRP during TKR, where the majority of studies reported significant benefits with regard to improving post-operative blood loss, length of stay and pain ratings. However, most of these small studies recommended the performance of larger studies to verify and confirm these findings.

PRP has also been extensively studied in neurosurgery, especially spinal fusion. Several small RCTs have been published investigating the use of PRP for improving fusion rates (Carreon, 2005; Feiz-Erfan, 2007; Hee, 2003; Weiner, 2003), none of which reported any significant benefit from PRP use.

In 2012, Hua and others reported the results of a randomized, non-blinded study of PRP vs. Nd-YAG laser treatment for benign cervical ectopy (n=60 in each group). The authors reported complete cure rates of 93.7% for the PRP group and 92.4% for the laser group (p>0.05). Mean time to re-epithelialization was significantly shorter in the PRP group (6.41 ± 2.05 weeks) than in the laser group (8.28 ± 1.72 weeks) (p<0.01). They also noted that the rate of adverse treatment effects (i.e., vaginal discharge or vaginal bleeding) was much lower in the PRP group than in the laser group (p<0.01) and the effects were milder. Eleven subjects in the PRP group had mild or moderate vaginal bleeding after treatment but none had heavy bleeding and of the 25 subjects with vaginal bleeding in the laser group, 2 had heavy bleeding necessitating tamponade. The results of this study are interesting; however, this is the first report in the literature of PRP used for this indication. Further study is warranted.

According to the American Urological Association (AUA) guideline for erectile dysfunction (AUA, 2018), the committee states that PRP therapy for men with erectile dysfunction should be considered experimental (expert opinion). In 2021 the Sexual Medicine Society of North America (SMSNA) published a position statement on restorative therapies for erectile dysfunction. The society concluded that “platelet rich plasma is experimental and should only be conducted under research protocols in compliance with Institutional Review Board approval”.

Overall, the body of data regarding potentially beneficial use of PRP for any condition is of poor quality and of limited use. Large well-designed trials are needed to effectively evaluate the use of PRP in the clinical setting.

Bone Marrow Aspirate Concentrate

The use of bone marrow aspirate concentrate (BMAC) has been proposed for several conditions, including for the treatment of critical limb ischemia (CLI). At this time, there is limited evidence available in the peer-reviewed published literature addressing BMAC. The published studies include a few small RCTs (de Girolamo, 2019; Iafrati, 2013; Powell, 2011) and several other small studies addressing various conditions including, but not limited to CLI (Kolvenback, 2010) and knee osteoarthritis (Centeno, 2018; Rodriguez-Fontan, 2018).

The RCT reported by Iafrati (2013) was double-blind and involved 48 subjects assigned to undergo treatment with BMAC (n=34) or sham (n=14). The authors noted that this pilot study was not powered to demonstrate statistical significance. However, they did note favorable trends for BMAC vs. control in major amputations (17.6% vs. 28.6%), improved pain (44% vs. 25%), improved ankle brachial index (32.4% vs. 7.1%), improved Rutherford classification (35.3% vs. 14.3%), and quality-of-life scoring better for BMAC in 6 of 8 domains. No adverse events were attributed to the injections and renal function was not reported to have been affected.

In 2011, Powell reported the interim results of the RESTORE-CLI study, which was a randomized, double-blind, sham controlled trial. The study compared treatment of CLI of the lower limbs with either autologous bone marrow aspirate vs. sham treatment. The plan was to enroll 150 subjects randomized in a 2:1 fashion. This interim report provided data on 33 subjects who completed the 12-month study period and another 13 subjects who had reached the 6-month follow-up visit (n=46 total, n=32 autologous group, n=14 controls). The authors reported that there was no difference in adverse or serious adverse events between groups. The statistical analysis revealed a significant increase in time to treatment failure (p=0.0053) and amputation-free survival in subjects receiving autologous treatment (p=0.038). Major amputation occurred in 19% of autologous-treated subjects compared to 43% of controls (p=0.14). There was evidence of improved wound healing in the autologous-treated subjects when compared with controls at 12 months. Following this interim analysis, this study was halted due to a positive efficacy signal and the sponsor's plan to develop a phase III program.

In a randomized controlled trial, Centeno and colleagues (2018) compared a protocol of bone marrow concentrate (BMC) combined with platelet products to exercise therapy for moderate (grade II or III) knee osteoarthritis. A total of 48 participants were randomized to either receive image-guided injections of BMC containing mesenchymal stem cells and platelet products (n=26) or a home exercise therapy program (n=22). Outcome measurements included vital signs, physical exam and self-reporting. Those in the exercise group were allowed to cross over to BMC injection therapy after 3 months. Participants in the injection and crossover groups received a pre-treatment injection, bone marrow aspiration, BMC with platelet injection, and a post-treatment injection. No serious adverse events were reported, and the most common complaint after treatment was pain (recurrent knee pain was treated with plasma injections at the discretion of the physician). At 3 months, the injection group (n=24) showed significant improvement over the exercise group (n=22) for lower extremity activity scale (LEAS) and KSS-knee scores, but there were no differences for visual analog scale (VAS) pain, KSS-function, SF-12, or range of motion. At 3 months, all participants in the exercise group crossed over to the injection therapy group; however, after 3 months, 4 withdrew voluntarily, 7 were withdrawn by the investigator, and 3 were withdrawn to have a total knee replacement. Outcome scores, except for SF-12 mental health, remained significantly improved in the injection and crossover participants at 2 years compared to baseline. The study was limited by its small size and limited follow-up with a crossover at 3 months.

Further studies are needed to fully assess the safety and efficacy of BMAC therapy for any condition.

Autologous protein solution

APS, also known as autologous white blood cell concentrate, is a product produced from an individual's blood to create a solution of concentrated anti-inflammatory cytokines and anabolic growth factors. The nStride APS kit (Biomet Biologics, Warsaw, IN) has been proposed as a tool to create APS for intra-articular treatment of osteoarthritis of the knee. There are currently a limited number of published peer-reviewed studies describing clinical outcomes related to the administration of APS produced with the nStride kit. The first study, by van Drumpt (2016), was a case series study involving 11 subjects with early to moderate osteoarthritis of the knee who were treated with APS and followed for 6 months. No serious adverse events or adverse events related to APS treatment were reported. The mean WOMAC composite scores and pain, stiffness, and function subscale scores all showed significant improvement compared to baseline by 2 weeks post-injection ($p<0.001$). Continued improvement was reported through 3 months ($p<0.05$) and stable through 6 months. A second study, reported by Hix and colleagues (2017), was another case series study involving 11 subjects with early to moderate osteoarthritis of the knee who were treated with APS and followed for 12 months. Only mild adverse events were reported, with three cases of arthralgia and one case of musculoskeletal discomfort. All cases resolved within 6 days. At 1 year, WOMAC pain scores were reported to be significantly improved, with a 72.5% improvement in pain on average ($p<0.0001$). Similarly, WOMAC stiffness, function, and total scores were also significantly improved ($p<0.037$, $p<0.0064$, and $p<0.0064$, respectively). At all time points, Knee Injury and Osteoarthritis Outcome Score (KOOS) measures were significantly improved, including measurement scales for pain ($p<0.0029$), symptoms ($p<0.0269$), stiffness ($p<0.0420$), function ($p<0.0050$), and sport function ($p<0.0231$). The most recent and largest study reported was an RCT published by Kon (2018) involving 46 subjects with moderate osteoarthritis of the knee randomized to receive a single ultrasound-guided injection of APS (n=31) or saline (n=15). Subjects were followed for 12 months, where improvement in WOMAC pain score was reported to be 65% in the APS group vs. 41% in the saline group ($p=0.02$). No significant differences between groups with regard to VAS pain scales were noted. At 12 months, the APS group showed improved SF-36 Bodily Pain subscale ($p=0.0085$) and Role Emotional Health subscale ($p=0.0410$), as well as CGI-C values ($p=0.01$) compared with saline controls. Significant differences between groups were also detected in change from baseline to 12 months in bone marrow lesion size as assessed on MRI and osteophytes in the central zone of the lateral femoral condyle, both in favor of the APS group ($p=0.041$ and $p=0.032$, respectively).

These study results are promising, but additional data is needed to fully assess the safety and efficacy of the use of APS for any condition including knee osteoarthritis.

Background/Overview

Overview

Stem cell therapy, a component of regenerative medicine, involves the insertion (usually an infusion or injection) of stem cells into the body to repair body tissues. Sources of stem cells include a person's own stem cells (such as those extracted from blood and tissues), another person's stem cells, stem cells extracted from embryos, and stem cells extracted from pregnancy remains (amniotic fluid, placentas, umbilical cords or umbilical cord blood).

Stem cells are unspecialized cells that have the unique ability to self-renew through cell division or differentiate into specialized cells, such as red blood cells, brain cells, or muscle cells. They form the human body and replace damaged cells throughout a person's lifespan. Stem cells are divided into four main classes: totipotent, pluripotent, multipotent, and unipotent.

Totipotent stem cells can form every cell type in the body, including placental and umbilical cord cells. The first cell of human life, the zygote, is a totipotent stem cell that divides to create more totipotent stem cells. After the first few days of embryonic development, totipotent stem cells cease to exist and give rise to pluripotent stem cells.

Pluripotent stem cells can form every cell type in the body except umbilical and placental cells. They are found in 3- to 5-day old embryos called blastocysts. Additionally, some pluripotent cells are found in fetal tissue after 8 weeks of development. Due to ethical concerns, the use of embryonic stem cells (totipotent and pluripotent) and fetal tissue stem cells for stem cell therapy has been controversial in the United States, with some states banning or limiting research. As an alternative, researchers have been working on the creation of induced pluripotent stem cells (iPSCs), which are specialized adult human cells reprogrammed to act like pluripotent embryonic stem cells. iPSCs are still in the investigative stages, and more research is needed before they can be used for stem cell therapy.

As human development continues, pluripotent cells cease to exist and give rise to multipotent stem cells that stay in the body throughout life. Multipotent stem cells form certain specialized cell types, usually the types needed to repair the tissue or organ where they reside, although some research suggests they may be able to transdifferentiate into other cell types. Multipotent stem cells can give rise to unipotent stem cells, which differentiate along only one lineage.

Multipotent and unipotent stem cells are referred to as adult stem cells (also called tissue-specific cells or somatic cells) and are found in many areas of the body. They are thought to reside in a specific location in the tissue called the "stem cell niche." Researchers have identified many types of adult stem cells, including neural, epithelial, epidermal, hematopoietic, and mesenchymal. Currently, hematopoietic adult stem cell therapy for transplants is the only established use of stem cells. Researchers are investigating other types of adult stem cells, with the largest focus on mesenchymal stem cells.

Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are non-hematopoietic, multipotent stem cells that can differentiate into a variety of cell types. The four major cell types are osteocytes (bone), myocytes (muscle), adipocytes (fat) and chondrocytes (cartilage). MSCs have immunomodulatory properties and secrete cytokines. MSCs remain in a quiescent (non-proliferative) state during most of their lifetime, pending stimulation by the signals triggered by tissue renewal, damage and remodeling processes. Because of their multi-lineage potential, immunomodulatory properties and ability to secrete anti-inflammatory molecules, MSCs may have the potential to treat various chronic autoimmune, inflammatory and degenerative diseases (Ullah, 2015).

MSCs have been isolated from various sites, including dermis, amniotic fluid, adipose tissue, endometrium, dental tissue, synovial fluid, placenta and umbilical cord tissue. Additionally, researchers have been able to culture hMSCs in specific media. The MSC population in red bone marrow is estimated at 1 per 10^5 nucleated cells. The incidence

of MSCs in adults is 1 per 10^3 nucleated cells (Piccirilli, 2017). Counts in cord blood or peripheral blood are lower (Bonab, 2006). These tissue sources differ with respect to MSC cell density and differentiation capacity. Bone marrow-derived MSCs are considered the preferred source for bone repair and regeneration as there is better chondrogenic differentiation potential (Shao, 2015). Although other sources for MSCs have been identified, the bone marrow is currently the primary source of procurement.

MSC therapy has been proposed as a treatment option for orthopedic indications that include torn cartilage, osteoarthritis, and bone grafting. The proposed benefits of MSC therapy are improved healing and possible avoidance of surgical procedures with protracted recovery times. MSCs are used as a stand-alone therapy in the form of an injection or in combination with scaffolds (Viganò, 2016).

Optimal materials or grafts that promote bone growth and healing require the following properties (Shen, 2005):
- Osteogenic: contains osteoprogenitor cells that can lay down a new bone matrix
- Osteoinductive: provides signals required to induce differentiation of MSCs into mature osteoblasts
- Osteoconductive: passive scaffolding to promote vascular invasion and bone apposition on the surface for new bone formulation

Currently, the risks of MSC therapy for the treatment of chronic, autoimmune, inflammatory and degenerative conditions are unknown. Insufficient data have been reported to allow a proper understanding of how this technology may affect individuals either in the short or long-term. Furthermore, there are known risks related to the various methods utilized to harvest MSCs from the bone marrow, including pain and hemorrhage.

MSC therapy is being investigated as a treatment of many chronic, autoimmune, inflammatory, severe pulmonary syndrome and degenerative conditions, including but not limited to the following diseases:
- Alzheimer's Disease: An irreversible and progressive form of dementia that causes difficulty with memory, thinking and behavior. Symptoms generally develop slowly and worsen over a number of years, eventually becoming severe enough to interfere with tasks. In its early stages, memory loss is mild, but with late-stage Alzheimer's, individuals are unable to carry on a conversation and respond to their environment. While there is no cure for Alzheimer's disease or a way slow its progression, there are drug and non-drug options that may ameliorate symptoms.
- Amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease): A group of rare neurological diseases that primarily involve the nerve cells responsible for controlling voluntary muscle movement. Early symptoms of ALS generally include stiffness or muscle weakness. Gradually all muscles under voluntary control are affected, and the person loses his/her strength and the ability to move, eat, speak and even breathe. The majority of individuals with ALS die from respiratory failure, usually within 3 to 5 years from when the symptoms first appear. However, approximately 10% of people with ALS survive for 10 years. Currently, there is no cure for this condition and no effective treatment to stop or reverse the progression of the disease.
- Celiac Disease: An autoimmune disease in which the small intestine becomes hypersensitive to gluten, leading to difficulty in digesting food. Currently, the only treatment for celiac disease is lifelong avoidance of foods with gluten in it (for example, wheat, rye and barley).
- Coronavirus disease 2019 (COVID-19): An infectious disease caused by a newly discovered coronavirus. In the older population and those with underlying medical conditions serious illness may develop. Serious symptoms may include difficulty breathing or shortness of breath, chest pain or loss of speech or movement.

Currently there is not a specific treatment for the virus; individuals who become sick may be treated with supportive measures.

- Crohn's Disease: A chronic inflammatory condition affecting the lining of the gastrointestinal tract. Crohn's disease can lead to abdominal pain, severe diarrhea, weight loss, fatigue and malnutrition. The inflammation caused by Crohn's disease can involve different areas of the digestive tract in different individuals. People with Crohn's disease may experience severe symptoms followed by periods of no symptoms. There is currently no cure for Crohn's disease. Medical treatment is typically focused on reducing the inflammation that triggers signs and symptoms and improving long-term prognosis by limiting complications.
- Multiple Sclerosis: A chronic and generally progressive, autoimmune disease in which the sheaths of nerve cells in the brain and spinal cord are damaged. The effects of multiple sclerosis varies between affected individuals. Symptoms may include impairment of speech and of muscular coordination, numbness, blurred vision, and severe fatigue. There is no cure for multiple sclerosis. Treatment may focus on slowing the progression of the disease, speeding recovery from attacks, and symptom management.
- Osteoarthritis: A degenerative condition caused by inflammation, breakdown, and eventual loss of cartilage in the joints. Osteoarthritis most commonly affects joints in the knees, hands, hips and spine.
- Parkinson's Disease: A neurodegenerative disorder that affects predominately dopamine-producing neurons in the substantia nigra of the brain. Individuals with Parkinson's disease may experience tremors in a limb (often the fingers or hand). The disorder causes slowness of movement and may also cause stiffness, loss of balance, as well as slurred or slowed speech. There is no cure for Parkinson's disease, but treatments include medications, surgical therapy and lifestyle modifications.
- Systemic Lupus Erythematosus: An inflammatory, disease caused by the immune system attacking its own tissues. Inflammation caused by lupus may affect many different areas of the body including but not limited to the skin, joints, kidneys, brain, blood cells, heart and lungs. Treatment for systemic lupus erythematosus is generally focused on easing the symptoms and will vary depending on how severe the symptoms are and which areas of the body are affected. The goal of treatment is to ease symptoms. Treatment varies depending on the symptoms and the affected areas of the body. Currently, there is no cure for systemic lupus erythematosus.

Bone Marrow Mononuclear Cell and Peripheral Blood Mononuclear Cell Therapies

Several medical conditions, including diabetes, TAO (also known as Buerger's disease) and ASO, are known to lead to damage to the arteries and other blood vessels leading to the extremities. These conditions, collectively referred to as PVD, which is also known as peripheral artery disease (PAD), lead to impaired blood flow and oxygen delivery to the hands and feet, and eventually to tissue damage. In most cases, this condition is treated with surgical revascularization. However, in extreme cases surgery is not an option and a condition known as CLI develops. This leads to severe tissue damage and the only treatment option left is limb amputation.

Stem cell therapy has been proposed as a treatment for PVD. The theory is that implantation of stem cells from the bone marrow into the affected limbs could trigger the growth of new blood vessels, increasing blood flow to the extremities and treating complications that develop due to PVD. At this time, two approaches for stem cell therapy for PVD have been described in the medical literature. The first involves the direct harvesting of BMMNCs from the bone marrow. The other method involves administering a hormone called Granulocyte-Colony Stimulating Factor (G-CSF) to the person to be treated. This stimulates the bone marrow to produce mononuclear stem cells and release them into the blood stream. These cells, now called PBMNCs, are then collected as part of a blood sample

collected from a vein. Regardless of the type of cells used, the collected stem cell samples are processed to isolate and multiply the cells, which are then transplanted back into the person being treated. Several different transplantation methods have been described in the scientific literature, including injection into a vein, artery, or muscle of the affected limb.

At this time the use of stem cell therapy for PVD is in the preliminary stages of investigation. There is much yet to be understood about this medical procedure before it should be widely used.

There are several products or services proposed for the processing of stem cells for PVD treatment, including the VesCell (TheraVitae, Bangkok , Thailand), and the MarrowStim P.A.D. kit™ (Biomet Biologics, Warsaw, Indiana).

Autologous Cell Therapy

From a basic science viewpoint, it must be shown that autologous cells, when transplanted into an organ such as the heart, can (1) truly regenerate myocardium by incorporating themselves into the native tissue, surviving, differentiating, and ultimately electromechanically coupling to each other, or (2) serve as a trophic factor leading to survival of injured myocardial tissue and improved cardiac function through tissue preservation and ventricular remodeling. For example, preliminary studies have suggested that transplanted myoblasts are potentially capable of producing disorderly or irregular heart rhythms.

ACT for the treatment of damaged heart muscle involves the transplantation of various types of cells into a damaged heart with the goal of replacing damaged heart muscle or to assist in the healing process. Various types of ACT have been researched to either stimulate regeneration of the heart muscle or modify ventricular remodeling post-infarct. For example, it is thought that after an MI an increased number of hematopoietic stem cells are released into the circulation and then engrafted into the heart.

In humans, skeletal myoblasts, harvested from a muscle biopsy, or hematopoietic stem cells, harvested from the bone marrow or peripheral blood, or mesenchymal stem cells, harvested from the bone marrow have also been investigated as cell sources for ACT. The harvested cells can be transplanted in a variety of ways, frequently as an adjunct to coronary artery bypass surgery; for example, either by injecting directly into the nonfunctional heart muscle, or injecting into a coronary artery or coronary sinus. It is thought that through the release of chemokines released by the heart, circulating hematopoietic stem cells might have a natural homing ability to reach damaged myocardium.

The proposed benefits of ACT for the treatment of damaged myocardium are improved heart function, restored myocardial viability and potentially extended lifespan. However, several of the published clinical trials report physiological measures as intermediate outcomes; hence, it is uncertain how this technology may improve net health outcomes. In addition, there are known risks related to the various methods utilized to harvest and transplant autologous cells, including pain, hemorrhage, cardiac arrest, and death.

ACT is a novel medical treatment that has become a rapidly evolving field being investigated over the last few decades. ACT treatment includes transplantation of various types of cells harvested from the individual and then returned to them in a unique manner. This treatment may involve one or several types of cells and has been

proposed for a wide variety of conditions including but not limited to, orthopedic, rheumatologic and vascular applications.

Other Adult Stem Cell Types

In addition to mesenchymal stem cells, researchers have identified other adult stem cell types in the body. Examples include:

- Hematopoietic stem cells – give rise to all types of blood cells.
- Neural stem cells – give rise to nervous system cells, including nerve cells, astrocytes, and oligodendrocytes.
- Epithelial stem cells – give rise to digestive system cells, including absorptive cells, goblet cells, Paneth cells, and enteroendocrine cells.
- Epidermal stem cells – give rise to keratinocytes that form the skin's protective barrier.
- Follicular stem cells – give rise to cells that form hair follicles and the epidermis.

Challenges and Risks of Adult Stem Cell Therapy

While the concept of extracting and injecting adult stem cells may seem straightforward, scientists have identified many challenges and risks. Only limited numbers of adult stem cells are found in human tissues. They are difficult to isolate and do not self-renew in the laboratory as easily as embryonic stem cells. In addition, they are unpredictable and do not always differentiate into the desired cell type. Also, the intrinsic nature or external manipulation of stem cells can potentially form malignancies. There have been reports of unregulated stem cell therapy causing infection, blindness, tumor growth, paralysis, and the multiplication of an undesired stem cell type. As stem cell research continues, scientists are working on ways to mitigate these challenges and risks (FDA, 2019; NIH, 2018).

Regulation

The U.S. Food and Drug Administration (FDA) regulates tissues and human cells intended for implantation, infusion or transplantation via the Center for Biologics Evaluation and Research, under Code of Federal Regulation, title 21, parts 1270 and 1271. Currently, the only stem cell products approved by the FDA are hematopoietic progenitor cells from umbilical cord blood. In 2017, the FDA issued a warning to consumers stating some medical providers are using unapproved and unproven stem cell treatments that may be dangerous. They stated that to ensure safety, stem cell treatments should be FDA-approved or have an Investigational New Drug Application (IND), which is a clinical investigation plan the FDA has allowed to proceed.

Definitions

Autologous: A product derived from the individual's own body or body products.

Autologous conditioned plasma (ACP): A type of PRP, which is distinguished from other PRP products by a low concentration of white blood cells that may be detrimental to the healing process when present in high concentrations.

Autologous cell therapy (ACT): A medical treatment involving the transplantation of various types of cells harvested from the individual and then returned to them in a unique manner. This treatment may involve one or several types of cells and has been proposed for a wide variety of conditions.

Bone marrow mononuclear stem cells: A type of bone marrow-derived cell from which blood vessels are created and repaired.

Differentiation: The multi-stage process by which an unspecialized stem cell gives rise to specialized cells.

Exosomes: Small, double-lipid membrane vesicles that are secreted from cells and encapsulate a portion of the parent cell cytoplasm. Exosomes shed into biofluids, including blood and urine.

Growth factors: Products that play important roles in the regulation of cell division and tissue propagation.

Hematopoietic stem cells: A type of cell from which blood cells are created.

Human-derived autologous wound factor gel (e.g., Aurix, Vitagel): A product that is derived from blood taken from an individual to create a platelet-rich plasma preparation for the treatment of wounds.

Mesenchymal stem cells: A type of bone marrow derived cell from which muscles are created. It is a term that is currently used to define non-blood adult stem cells from a variety of tissues, although it is not clear that mesenchymal stem cells from different tissues are the same.

Multipotent: Possessing the ability to produce more than one type of specialized cell of the body, but not all types of cells.

Myocardium: The medical term for the heart muscle.

Platelet rich plasma (PRP): A preparation made of concentrated platelets from autologous blood; this substance has been suggested for use to improve healing for a wide variety of medical conditions.

Progenitor cells: Primitive cells capable of replication, differentiation and formation into mature cells.

Remodeling: The overstretching of viable cardiac cells to maintain cardiac output.

Skeletal myoblasts: A type of cell from which skeletal muscle fibers are created.

Stem cells: A type of self-renewing cell from which other types of cells develop.

Stem cell therapy: A medical treatment that involves the implantation of stem cells into the body with the goal of growing new or repairing damaged or defective tissues and organs. This type of treatment has been proposed for a wide variety of conditions, including Parkinson's disease, heart disease, and spinal cord injury.

Transdifferentiation: The ability for adult stem cells to give rise to specialized cells other than those expected by the stem cell's lineage.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
When the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT	
0232T	Injection(s), platelet rich plasma, any tissue, including image guidance, harvesting and preparation when performed
0263T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; complete procedure including unilateral or bilateral bone marrow harvest
0264T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; complete procedure excluding unilateral or bilateral bone marrow harvest
0265T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; unilateral or bilateral bone marrow harvest only for intramuscular autologous bone marrow cell therapy
0481T	Injection(s), autologous white blood cell concentrate (autologous protein solution), any site, including image guidance, harvesting and preparation, when performed
0748T	Injections of stem cell product into perianal perifistular soft tissue, including fistula preparation (eg, removal of setons, fistula curettage, closure of internal openings)
17999	Unlisted procedure, skin, mucous membrane and subcutaneous tissue [when specified as harvesting or administration of stem cells for therapy to repair damaged cells or body tissues]
20999	Unlisted procedure, musculoskeletal system, general [when specified as harvesting and injection of bone marrow aspirate concentrate or harvesting or administration of stem cells for therapy to repair damaged cells or body tissues]
33999	Unlisted procedure, cardiac surgery [when specified as autologous cell therapy for damaged myocardium, including harvesting and preparation of cells]
38999	Unlisted procedure, hemic or lymphatic system [when specified as bone marrow cell therapy or stem cell therapy such as IM, IV or IA for peripheral vascular disease]

64999	Unlisted procedure, nervous system [when specified as harvesting or administration of stem cells for therapy to repair damaged cells or body tissues]

HCPCS

G0460	Autologous platelet rich plasma for non-diabetic chronic wounds/ulcers, including phlebotomy, centrifugation, and all other preparatory procedures, administration and dressings, per treatment [for example, Aurix]
G0465	Autologous platelet rich plasma (PRP) for diabetic chronic wounds/ulcers, using an FDA-cleared device (includes administration, dressings, phlebotomy, centrifugation, and all other preparatory procedures, per treatment) [for example, Aurix gel] Note: HCPCS code P9020 Platelet rich plasma, each unit is not specific to autologous PRP; if used to describe autologous PRP it would be considered investigational and not medically necessary

ICD-10 Diagnosis

All diagnoses

When services are also Investigational and Not Medically Necessary:
When the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

	For the following procedures when specified as harvesting or administration of stem cells for therapy to repair damaged cells or body tissues:
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous

ICD-10 Procedure

30233AZ	Transfusion of embryonic stem cells into peripheral vein, percutaneous approach
30243AZ	Transfusion of embryonic stem cells into central vein, percutaneous approach
3E0Q0AZ	Introduction of embryonic stem cells into cranial cavity and brain, open approach
3E0Q3AZ	Introduction of embryonic stem cells into cranial cavity and brain, percutaneous approach
3E0R0AZ	Introduction of embryonic stem cells into spinal canal, open approach
3E0R3AZ	Introduction of embryonic stem cells into spinal canal, percutaneous approach
6A550ZV	Pheresis of hematopoietic stem cells, single

ICD-10 Diagnosis

	Including, but not limited to, the following:
E08.51-E08.59	Diabetes mellitus due to underlying condition with circulatory complications

E09.51-E09.59	Drug or chemical induced diabetes mellitus with circulatory complications
E10.51-E10.59	Type 1 diabetes mellitus with circulatory complications
E11.51-E11.59	Type 2 diabetes mellitus with circulatory complications
E13.51-E13.59	Other specified diabetes mellitus with circulatory complications
G12.21	Amyotrophic lateral sclerosis
G20-G21.9	Parkinson's disease, secondary parkinsonism
G30.0-G30.9	Alzheimer's disease
G31.01-G31.9	Other degenerative diseases of nervous system, not elsewhere classified
G35	Multiple sclerosis
I70.201-I70.299	Atherosclerosis of native arteries of the extremities
I70.401-I70.499	Atherosclerosis of autologous vein bypass graft(s) of the extremities
I73.00-I73.9	Other peripheral vascular disease
K50.00-K51.919	Crohn's disease [regional enteritis], ulcerative colitis
K52.3	Indeterminate colitis
K90.0	Celiac disease
M04.1-M04.9	Autoinflammatory syndromes
M15.0-M19.93	Osteoarthritis
M21.00-M21.079	Valgus deformity, not elsewhere classified
M21.10-M21.179	Varus deformity, not elsewhere classified
M21.70-M21.769	Unequal limb length (acquired)
M21.80-M21.869	Other specified acquired deformities of limbs
M21.90-M21.969	Unspecified acquired deformity of limb and hand
M23.000-M23.92	Internal derangement of knee
M24.10-M24.19	Other articular cartilage disorders
M24.20-M24.29	Disorder of ligament
M24.60-M24.69	Ankylosis of joint
M24.7	Protrusio acetabuli
M24.80-M24.89	Other specific joint derangements, not elsewhere classified
M24.9	Joint derangement, unspecified
M25.50-M25.59	Pain in joint
M32.0-M32.9	Systemic lupus erythematosus (SLE)
M75.00-M75.92	Shoulder lesions
M84.30XA-M84.9	Disorder of continuity of bone
M87.00-M87.9	Osteonecrosis
M91.0-M94.9	Chondropathies
S43.401A-S43.499S	Sprain of shoulder joint

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Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	11/10/2022	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Description, Rationale, Background, References, Websites and Index sections. Updated Coding section with 01/01/2023 CPT changes; added 0748T.
Revised	11/11/2021	MPTAC review. *Retitled policy:* Therapeutic use of Stem Cells, Blood and Bone Marrow Products. MED.00117 Autologous Cell Therapy for the Treatment of Damaged Myocardium content moved to TRANS.00035,

		INV/NMN statement clarified to include "for all indications". MED.00110 "Autologous Skin, Blood or Bone Marrow derived Products for Wound and Soft Tissue Applications" content moved into TRANS.00035. Updated Description, Scope, Rationale, Background, Definitions, References, Websites and Index sections. Updated Coding section; added 0232T, 0481T, G0460 previously addressed in MED.00110, 33999 NOC for autologous cell therapy for damaged myocardium previously addressed in MED.00117, and included 01/01/2022 HCPCS changes to add G0465.
	10/01/2021	Updated Coding section with 10/01/2021 ICD-10-PCS changes; removed open approach codes deleted 09/30/2021.
Reviewed	05/13/2021	MPTAC review. Updated Background, References and Websites sections. Updated coding section with corrected diagnosis range G31.01-G31.9.
	10/01/2020	Updated Coding section with 10/01/2020 ICD-10-CM changes; added M24.19, M24.29, M24.69, M24.89, M25.59.
Revised	05/14/2020	MPTAC review. Title changed to "Other Stem Cell Therapy." Position Statement revised from "non-hematopoietic adult stem cell therapy" to "stem cell therapy." Note in relation to scope added to Position Statement section. Updated the Description/Scope, Rationale, Background/Overview, Definitions, References, Websites for Additional Information, and Index sections. Updated Coding section to add codes 0263T, 0264T, 0265T, 38205, 38206, 6A550ZV and diagnosis codes previously addressed in TRANS.00036.
Revised	08/22/2019	MPTAC review. Title changed to "Non-Hematopoietic Adult Stem Cell Therapy." Position Statement expanded to include non-hematopoietic adult stem cell therapy. Updated the Description/Scope, Rationale, Background/Overview, Definitions, Coding, References and Websites for Additional Information sections. Added Index section.
Reviewed	03/21/2019	MPTAC review. Updated Rationale, Background/Overview, Definitions, References and Websites for Additional Information sections.
Revised	01/24/2019	MPTAC review. Title changed to "Mesenchymal Stem Cell Therapy for the Treatment of Joint and Ligament Disorders, Autoimmune, Inflammatory and Degenerative Diseases". Updated the Description/Scope, Rationale, Background/Overview, Definitions, References and Websites for Additional Information sections. Deleted Index section. Updated Coding section to include removing 20930 for spinal surgery no longer addressed.
Reviewed	09/13/2018	MPTAC review Updated Rationale and References sections.
Reviewed	11/02/2017	MPTAC review. The document header wording updated from "Current Effective Date" to "Publish Date." Updated Rationale, Background, References and Website sections.
	03/06/2017	Revised note in Scope section to clarify that TRANS.00035 addresses bone graft products with added or exogenous MSCs and that bone graft products with endogenous MSCs are addressed in CG-SURG-45.
Reviewed	11/03/2016	MPTAC review. Removed the products Osteocel, Trinity Evolution and Elite and BIO^4 from the rationale. Updated Description, Rationale, References, Website and Index sections.

Reviewed	08/04/2016	MPTAC review. Updated Description, Rationale, Background, References and Websites sections.
	04/01/2016	Updated Coding section with corrected diagnosis code range for spondylosis; also removed ICD-9 codes.
Reviewed	08/06/2015	MPTAC review. Updated Description/Scope, Rationale, Coding, References, Websites and Index sections.
Reviewed	08/14/2014	MPTAC review. Updated Description/Scope, Rationale, References and Websites sections.
Reviewed	08/08/2013	MPTAC review. Updated Rationale, Background, References and Websites sections.
Reviewed	08/09/2012	MPTAC review. Rationale, Background, References and Websites updated.
	01/01/2012	Updated Coding section with 01/01/2012 CPT changes.
Reviewed	08/18/2011	MPTAC review. Rationale, Background, References and Websites updated. Updated Coding section with 10/01/2011 ICD-9 changes.
Reviewed	08/19/2010	MPTAC review. Rationale, Background, References and Websites updated.
Reviewed	08/27/2009	MPTAC review. Rationale, websites and references updated.
New	08/28/2008	MPTAC review. Initial document development.