

Major Clinical Application of Adipose-Derived Stromal Cells

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Abstract:

In recent years, Adipose-Derived Stromal Cells (ADSCs) have emerged as a potent source of therapeutic cells for the treatment of various clinical indications. This review focusses on ADSCs as a product and the current clinical trial landscape of ADSCs. In-depth emphasis has been given for the clinical and conceptual framework of ADSCs to treat ischemic based indications such as Inflammatory Bowel Diseases, Cerebrovascular Diseases, Chronic Obstructive Pulmonary Disease, sclerosis based indications such as Amyotrophic Lateral Sclerosis, Multiple Sclerosis, Systemic Sclerosis, Crohn based Fistula, and Osteoarthritis.

Keywords: Adipose-derived stromal cells; Cell therapy; Clinical translation; Ischemia; Sclerosis; Crohn and Osteoarthritis based indications

Introduction

Pharmaceutical drugs modulate the human system to get cure from the diseases, but they rarely have the capacity to regenerate or restore the entire tissues. Many pharmaceutical drugs generally address only the relief from debilitating symptoms, but not the root cause of disease. Even when drugs are designed to address the root cause, their efficacy rate is unsatisfactory. For example the efficacy rate of drugs ranges from 30% to 62 % in diseases like Alzheimer's, Cardiac disease, Diabetes, Oncology, Osteoporosis, Rheumatoid arthritis, Schizophrenia etc^[1]. Furthermore, for new drugs, one in five has a chance of causing serious Adverse Drug Reactions (ADRs) and these reactions rank as the fourth main cause of death^[2-4]. Only 11 % to 15 % of newly approved drugs have a clinical advantage over existing prescription. Hence there is a need for alternatives to pharmaceutical drugs with better safety and efficacy.

One such alternative is cellular therapy which has the capacity to regenerate or restore the entire tissues. While drugs address a single target or disease-causing mechanism, cells by integrating multiple inputs and by acting through multiple, coordinated signals can regenerate or restore the entire tissues. Cells exert therapeutic effects because of their ability to hone to the site of injury, of their secretory activity, of their ability to differentiate into the required tissues and are safe. These properties of cells give them the ability to treat diseases which were previously untreatable. Hence attention is currently devoted to cell therapy to leverage its natural self-renewal and regenerative potential to develop as cell biologics.

Adipose derived uncultured cells as Stromal Vascular Fraction (SVF) and purified and expanded cells as Adipose-Derived Stromal Cells (ADSCs) are rapidly evolving in the field of regenerative medicine. Adipose tissue can be harvested easily with minimal discomfort to patients as opposed to bone marrow and with very few ethical concerns^[5]. The therapeutic mechanism of ADSCs lies in adjusting its functionality based on the microenvironment of diseased tissue, to repair, replace and regenerate for a targeted outcome. ADSCs have a tremendous self-renewal capacity and also secrete cytokines, exosomes and extracellular vesicles that aid in regeneration process^[6-8]. ADSCs demonstrate multi-lineage differentiation capabilities in both *in-vitro* and *in-vivo* modules^[9-11]. ADSCs also exhibit powerful hypoimmunogenic and immunomodulatory properties^[12]. This regenerative and immunotolerant profile of ADSCs make them an ideal candidate for various clinical applications.

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This review is focussed on using cultured ADSCs to address 4 major disease indications- Ischemia, Sclerosis, Fistula and Osteoarthritis where ADSCs can provide significant therapeutic benefits than traditional drugs. This review identifies the major gap and challenges of classical pharmaceutical drugs in clinics for these indications and emerging opportunity for the use of culture expanded ADSCs.

ADSCs as a product

Fat is an extremely promising rich source of stem cells. Since a small volume of liposuction is required for ADSCs isolation and expansion, it is relatively easy to perform without any complications compared to bone marrow aspiration. Various liposuction procedures like surgical resection, Power-Assisted Liposuction (PAL) and Laser-Assisted Liposuction (LAL) methodologies can be employed for harvesting adipose tissue. PAL provides higher yield, viability, proliferation ability, stable expression and prolonged culture of ADSCs compared to others^[13,14]. The ultrasound assisted liposuction procedures also provide similar ADSCs viability and yield without compromising on differentiation potential^[15]. The cost of PAL equipment is prohibitive for it to be used for adipose tissue harvesting in developing nations. Research is ongoing for the development of semi-automated or syringe based micro-lipoaspiration procedures for world-wide usability for small volume adipose tissue harvesting.

There are no standard isolation procedures and clear unified phenotypic markers to identify the therapeutic ADSCs from adipose tissue. Various enzymatic and non-enzymatic approaches have been utilized. The most common enzymes used for the adipose tissue digestion are collagenase, trypsin or dispase^[16]. Various enzymes, enzyme concentration, number of washing steps, centrifugation parameters, erythrocyte removal steps and incubation time period are utilized for the isolation of ADSCs. Enzyme digestion increases the cost and presents the risk of residuals in finished products. Non-enzymatic methodologies have shown high variability in cell yield and viability because of shear force, centrifugal, and pressure force^[17]. The manual enzymatic or non-enzymatic isolation procedures are tedious, non-scalable and prone to human error and contamination risk.

The automated and semi-automated whole cell isolation system were primarily designed for autologous fat grafting and later upgraded to isolation of cells from adipose tissue. There are several patented commercially available cell isolation systems that automate the SVF isolation process like AdiStem™ Sepax 2, Cellthera Kit I, Celution® 800 / CRS and 820 / CRS, GID SVF-1™ CHA STATION™ Icellator. These systems have a process time of around 65 to 120 mins^[18-19]. The SVF can be used as point-of-care cellular therapeutics and as potential to be used as a bio-surgical adjuvant.

From the SVF, the ADSCs are allowed to attach onto tissue culture flasks. The ADSCs are sequentially cultured in tissue culture flasks or in spinner flasks /bioreactors using micro carriers to get the required clinical dose^[20-22]. The feasibility of expanding ADSCs in controlled environment is clinically relevant to get consistent therapeutic effects and to maintain cGMP compliant production system.

While SVF from lipoaspirated fat have been utilized as

a therapeutic product in various diseases, cultured ADSCs are superior because of the reasons hence forth. The cellular subunit within the SVF varies from donor to donor and also from the site to site of the aspiration likely resulting in variable clinical outcome. Scale-up of purified, cultured, homogenous ADSCs from SVF generates quality tested, validated safe and efficacious products. Inability to obtain sufficient lipoaspirate compromises on the cell numbers per dose in SVF especially in lean donors. Further for multiple doses, repeat lipoaspirates are likely required. Expanded ADSCs allow for constant cell dose availability and requires only single small volume lipoaspirate even for repeat doses. Cultured ADSCs can be primed to increase the intended therapeutic efficacy. For example *in-vivo* chondrogenic potential can be improved through hypoxic preconditioning of ADSCs, which is not possible in SVF^[23]. Cryopreserved SVF for repeat doses, has significantly reduced stability and post-thaw proliferation efficiency. Expanded ADSCs can be cryopreserved which maintains stability and viability. Pure population of ADSCs allow us to perform controlled *in-vitro* and pre-clinical safety, mechanistic and efficacy studies in support of therapeutic *in-vivo* applications^[24-25]. Variation in SVF poses limitation for such studies. Expanded ADSCs generates off-the-shelf allogeneic products, while still allowing for autologous procedures. Multiple expanded ADSCs can be screened to select one with maximum therapeutic potential. SVF cannot be used for allogenic purpose.

The screening and selection framework to find therapeutic ADSCs is similar to screening and selection of therapeutic candidates in biopharmaceutical sector^[26,27]. Hence ADSCs can easily adopt the industrial scale-up and commercialization techniques from biopharmaceutical sectors. Expanded ADSCs can be used in various tissue engineered medicinal products. In addition, ADSCs / differentiated ADSCs can be used as *in-vitro* toxicological platforms for safety / drug testing^[28]. On the other hand, expanded ADSCs can be used to produce products similar to Progenza (allogeneic ADSCs from Regeneous). The process of generating similar cell therapeutics allows shortening of clinical testing phase, time and investment.

Globally, Mesenchymal Stem Cells (MSCs) have been used as approved products as well as in several clinical trials. The approved products include Autologous modalities such as CupiStem (ADSCs), Hearticellgram AMI (BM - MSCs), CardioRel (BM - MNCs) and Allogeneic modalities like CARTISTEM (UB - MSCs), Prochymal (BM - MSCs), AlloStem (BM - MSCs + Bone Matrix), Trinity Evolution (MSCs + Bone matrix). Other MSCs based products are in near approval and some are in late stage clinical trials^[29]. The above standard MSCs based products provide a clear road-map for the development and commercialization of ADSCs based products.

Landscape of ADSCs clinical trials

Search on Clinicaltrials.gov reveals that SVF and ADSCs have been used in 253 registered trials. Among the 253 trials, only 64 trials (25 %) were completed. The 61 (24.01 %) clinical trials are industry sponsored trials and rest are non-industry sponsored trials. The 11 trials (4.34 %) were withdrawn or terminated for unknown reasons. Active clinical trials are 136 in number (53.75 %) and the remaining 42 clinical trials (16.6 %) are of unknown status. The major clinical indications

of ADSCs used by industry and non-industry group was plotted in [Figure. 1] and the status of industry sponsored clinical trial for development of adipose based product was tabulated in [Table.1] Non-industry sponsors like clinics, academics, hospitals, university hospitals contributed to the majority stake (82) in using ADSCs for clinical translation compared to industry-sponsored trials (26 firms). The majority of the clinical trials were ischemic based indications (Inflammatory Bowel Diseases, Cerebrovascular Diseases, Chronic Obstructive Pulmonary Disease), sclerosis based indications (Amyotrophic Lateral Sclerosis, Multiple Sclerosis, Systemic Sclerosis), Crohn based fistula and Osteoarthritis. Here we have attempted to review clinical applications of adipose cell-based therapy for these indications based on rationale, and conceptual approach.

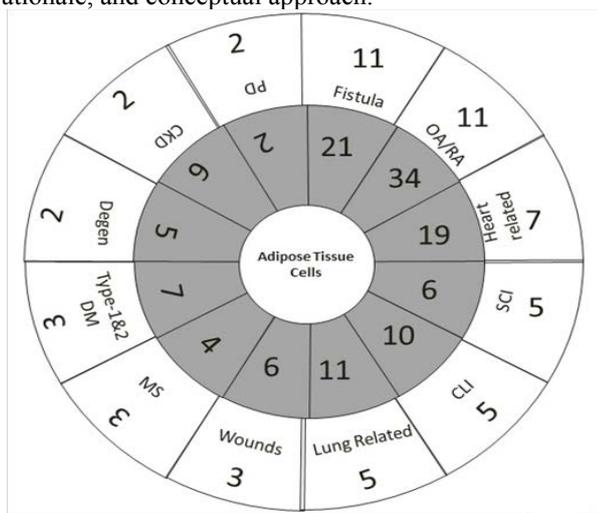


Figure 1: Various clinical trial indications based on industry priority scale from 5 min to 60 min clock. Inner circle indicates a total number of clinical trials of particular indications, whereas outer circle provides industry sponsored clinical trials for particular indications.

Abbreviations: CKD-Chronic Kidney Disease; CLI-Critical Limb Ischemia; Degen-Degenerative Diseases; MS-Multiple Sclerosis; OA: Osteoarthritis; PD-Pulmonary Disease; RA-Rheumatoid Arthritis; SCI-Spinal Cord Injuries.

Table 1: Industry sponsored clinical trials using adipose-based cells as biologics.

Abbreviations: Allo-Allogeneic; AMI-Acute Myocardial Infarction; Auto-Autologous; AZ-Alzheimer’s Disease; DM-Diabetes Mellitus; ED-Erectile Dysfunction; PD-Parkinson’s Disease; SCI-Spinal Cord Injury; P1-Phase 1; P2-Phase2; NA-Not Available; UK-Status Unknown

Company Name	Biologicals	Indications	Phase
AdiSave Inc.	ADSc-SVF	Abnormally Healing Wounds Scars Soft Tissue Defects	P1
Adistem Ltd	Auto-AD-SVF	Type-1 DM	P1
	Auto-AD-SVF	Type-2 DM	P1
Ageless Regenerative Institute	Auto-AD-SVF	CLI, PD,ED, COPD, Type-2 DM, MS, AZ, OA	P1
	Auto-AD-SVF	FISTULA, STROKE, AMI	P1
American Cryo Stem Corporation	Auto-ADSCs	MS	P1

Anterogen Co., Ltd.	Auto-ADSCs (low dose)	Complex Perianal Fistula	P2
	ADIPOPLUS	Crohn’s Fistula, Crohn;s Disease, Fistula	P2
	Allo-ADSCs	Crohn, Tennis Elbow	P1
	Auto-ADSCs (ANT-SM)	Fecal Incontinence	P1
	Auto-ADSCs	Perianal Fistula Primary; Complex	P1
	Allo-ADSC -DFU	Burn	P1
	Allo-ADSC -DFU	Crohn’s Disease	P1
	Allo-ADSC -DFU	Diabetic Foot Ulcer	P1
	Adipocell	Depressed Scar	P1
	Repaircell	Healthy	P2 / P3
Antria	SVF	Lipoatrophy Aging Wrinkles	P1
	Liposuction	Soft Tissue Mass Removal	P1
	SVF	Facial Atrophy	P2
Bioheart, Inc.	Auto-ADSCs	Dry Macular Degeneration	NA
	Auto-ADSCs	Degenerative Disc Disease	NA
	Auto-ADSCs	COPD	NA
Biostar	RNL-Vas-costem®	Buerger’s Disease	P1 / P2
	Auto-ADSCs	SCI	P1
	Auto-ADSCs	Degenerative Arthritis	P1 / P2
	Auto-ADSCs	Degenerative Arthritis Knee OA	UK
	Auto-ADSCs(-JOINTSTEM)	Degenerative Arthritis Knee OA	P2
	Auto-ADSCs	Progressive Hemifacial Atrophy Romberg’s Disease	P2
	Auto-ADSCs	SCI	P1 / P2
	Auto-ADSCs	Lumbar Intervertebral Disc Degeneration	P1 / P2
	Auto-ADSCs	CLI	P1 / P2
	Auto-ADSCs	Avascular Necrosis of the Femoral Head	P1 / P2
Bukwang Pharmaceutical	Auto-ADSCs	SCI	P1
Cellerix	Auto-ASCs (Cx401)+Fibrin addisive	Anal Fistula	P3
	Auto-ADSCs	Complex Perianal Fistula Crohn Disease	P3
	Auto-ADSCs (Cx601)	Crohn’s Disease Anal Fistula	P1 / P2
	Auto-ASCs (Cx401)+Fibrin addisive	Complex Perianal Fistula	
	Non-surgical autologous implant of ASCs	Anal Fistula	P2

Cellular Bio-medicine Group Ltd	Auto-ADSCs (ReJoin™) Drug: Sodium Hyaluronate	Defect of Articular Cartilage Knee Osteoarthritis	P2
Elliot Lander Cell Surgical Network Inc.	SVF	Neurodegenerative Diseases OA Erectile Dysfunction Autoimmune Diseases Cardiomyopathies Emphysema	
Ferrer Internacional S.A. HistoCell S.L.	Allo-ADSCs (FAB117-HC)	Acute Traumatic Spinal Cord Injury	P1 / P2
Gwo Xi Stem Cell Applied Technology Co., Ltd.	Auto-ADSCs	Stroke	P1
	Auto-ADSCs	Liver Cirrhosis	P1
Healeon Medical Inc(Device: Centricyte)	SVF	RSD (Reflex Sympathetic Dystrophy) CRPS - Complex Regional Pain Syndrome Type I Fibromyalgia	P1 / P2
	SVF	IBD	P1 / P2
	SVF	Lung Disease	P1 / P2
	SVF	Multiple Sclerosis Autoimmune	
	SVF	Hair Disease	P1 / P2
InGeneron, Inc.	Auto-ADSCs	Rotator Cuff Tear - Partial Thickness	P1
JKastrup Rigshospitalet, Denmark	Allo-ADSCs	Heart Failure	P2
	Allo-ADSCs	Heart Failure	P1
Kasiak Research Pvt. Ltd.	SVF; Auto-ADSCs	Idiopathic Pulmonary Fibrosis	P1 / P2
	SVF; Auto-ADSCs	CLI	P1 / P2
Nature Cell Co. Ltd. KCRN Research, LLC	Auto-ADSCs (JointStem); Drug: Synvisc-One	OA	P2
StemGenex	SVF	Osteoarthritis	Uk
	SVF	Rheumatoid Arthritis	
	SVF	Chronic Obstructive Pulmonary Disease	
	SVF	MS	
	SVF	Parkinson's Disease	
Steminent Biotherapeutics Inc.	Auto-ADSCs	OA	P1
TiGenix S.A.U. Cellerix	Allo-ADSCs	Crohn's Disease	P3
	Allo-ADSCs	Sepsis	P1
	Allo-ADSCs	Localized Adverse Reaction to Administration of Drug	P1
	Allo-ADSCs	Rheumatoid Arthritis Aggravated	P1 / P2
Tissue Genesis, LLC (Cell Iso system device)	Auto-ADSCs; Device: ASC coated ePTFE vascular graft Device: Propaten graft	Lower Limb Ischemia	P1
Translational Biosciences	SVF	OA	P1
	SVF	Rheumatoid Arthritis	P1

Tri Phuoc Biotechnology, JSC	Device: Laminectomy Device: Intraduralspace Device: Intrathecal Device: Intravenous	Acute Spinal Cord Injury	P1
Unico Cell Biomed CO. LTD	Allo-ADSCs(Elixcyte)	Moderate to Severe Chronic Kidney Disease	P1
	Allo-ADSCs; Drug: Elixcyte Drug: Hya Joint Plus	Knee Osteoarthritis	P1

ADSCs Application for Major Disease Indications

Ischemia, Sclerosis, Fistula and Osteoarthritis are 4 major disease indications, where ADSCs can provide significant therapeutic benefits than traditional drugs.

Ischemic based indications

The shortage of blood supply and oxygen to any tissue due to narrowing of the local / regional blood vessels is termed as Ischemia. Applicability of ADSCs for some ischemic conditions namely Inflammatory Bowel Disease, Cerebrovascular Disease are reviewed.

Inflammatory Bowel Disease (IBD)

The IBD refers to a group of intestinal disorders arising due to the interaction of environmental and genetic factors that result in immunological responses and inflammation. The subgroup of IBD are (Intestinal ischemia or mesenteric ischemia or infarction) is the result of blockage of arteries supplying the intestine. Intestinal ischemia leads to bowel necrosis and perforation.

Incidences and prevalence

The Crohn's Disease (CD) and Ulcerative Colitis (UC) are two major types of IBD that occur in industrialized urban societies and have been considered as global emergence disease^[30]. Incidence of these diseases in previously considered low risk countries like India and Japan are rising due to changes in life-style, diet, life stress, smoking etc^[31]. There is a 50 % increase in mortality rate in CD compared to UC and 25 % - 50 % deaths are due to intestinal cancer, postoperative complications and malnutrition^[32].

Pathophysiology

The various pathophysiological events in IBD include activation of lymphocyte, phagocytes and pro-inflammatory cytokine leading to tissue destruction. The multifactorial cascading events following ischemia leads to oxygen depletion, abnormal epithelial barrier function leading to translocation of microbes and their products and inflammatory responses. Reperfusion to re-establish the blood flow generates the reperfusion injuries and reactive oxygen species (ROS); thereby ROS-mediated apoptosis and inflammatory cascade which further trigger multi-organ failure and death^[33].

Current treatment challenges

Current treatments involve induction and maintenance of remission using anti-inflammatory amniosalicylates and

corticosteroids, immunosuppressive agents, antibiotics, direct peritoneal resuscitation and biologic agents. Established anti-inflammatory agents, steroids and anticoagulation treatments after surgical resection of acute mesenteric ischemia (AMI) results in decreased necrosis nature. The long term results does not show satisfactory improvement^[33]. Conventional corticosteroid and new generation formulations have modest efficacy and are slow acting. The direct peritoneal resuscitation improved the survival rate after intestinal ischemia in animal models^[34]. The mortality rate for AMI was high as 40 %, when progressed towards surgical interventions^[35,36]. New biologics do not rise response rate to above 45 % to 60 % and the patients who respond to biologic treatment can lose response over repeat dose due to development of anti-drug antibodies^[37].

Mechanisms of Action of ADSCs for IBD

ADSCs promote functional recovery after injury, suppress inflammatory immunological cascade and secrete various paracrine and autocrine bio-factors to repair and regenerate the damaged site and hence would be ideal for IBD^[6,33,38,39]. ADSCs decreases apoptosis of injured cells, decreases intestinal permeability, increases the recovery of the gut mucosal barrier and increases neovascularization under hypoxic conditions^[40]. Transplantation of ADSCs in an animal model showed increased survival and improved outcome compared to keratinocytes as differentiated controls^[41]. Currently, there are very few clinical trials on IBD (NCT02952131) and are in recruiting phase. ADSCs application to IBD is an untapped therapeutic application and needs further proof of concept and rigorous dose finding studies in appropriate animal models.

Cerebrovascular disease

The cerebral arteries supplying oxygen to the brain are affected by cerebrovascular events such as stroke due to blockage or narrowing of arteries.

Incidences and prevalence

Cerebrovascular disease (CVD) is the second most leading cause of death after cancer^[42]. The 85 % of strokes are non-haemorrhagic ischemic strokes. Globally, around 16 million new cases are registered contributing to about 9.7 % of global deaths and expected to rase upto 7.8 million deaths by 2030. Incidence of CVD are rising due to change in diet habits, unchecked industrialization, smoking and alcohol consumptions^[43].

Pathophysiology

Reduced blood flow causes low energy availability and results in rapid failure of membrane ion gradient, thereby resulting in heavy influx of calcium into cells within minutes after the onset of ischemia. The exotoxic neurotransmitters like glutamate are released due to increased intra-cellular calcium levels, causing damage to neuronal cells. Then the onset of inflammatory cascade in peri-ischemic area with release of heat-shock proteins, proteinases, causes delayed release of remodeling proteins for healing^[44].

Current treatment challenges

Current treatment modalities include blood clot prevention and inhibition by heparin, warfarin, non-specific strepto-

kinase, urokinase, and tissue plasminogen activators. Non-specific digestion of thrombolytic therapies resulted in an allergic reaction and systemic bleeding or vascular lesions have been reported^[45]. Further, the plasma half-life of thrombolytic therapies including 3rd generation drugs like Tenecteplase, Reteplase is 15 to 20 minutes^[45]. These treatment modalities have failed to replace the surgical intervention to remove thrombus. Thus currently there are no effective drugs available as therapy to cure, regenerate the damaged tissue.

Mechanisms of Action of ADSCs for CVD

ADSCs can protect the neurons from cell death through secretion of VEGF, thereby promoting brain repair damage^[46]. ADSCs can promote functional recovery through neuronal differentiation by secreting several neurotrophic factors^[47]. ADSCs provide engraftment, differentiation and paracrine support and systemically administered cells have a shelf-life that is longer than a week^[48,49]. ADSCs have shown significant neural development and reversal of the cerebral ischemia in various animal studies. There are few clinical trials on acute ischemic stroke or stroke using adipose derived stromal cells and some are in phase-I (NCT01453829, NCT02813512) and phase-II (NCT01678534, NCT02849613) and the results are not yet published. ADSCs application to CVD is an untapped therapeutic application.

Chronic Obstructive Pulmonary Disease (COPD)

COPD is the development of progressive irreversible constriction of airways and destruction of lung parenchyma and lung elasticity without any pulmonary fibrosis.

Incidences and prevalence

Among lung diseases, COPD prevalence is increasing and they would be cause of world's 3rd disease mortality by 2030^[50]. Globally, COPD is the fourth leading cause of death affecting mainly people over 75 years and its prevalence range from 0.2 % to 37 % and varies from nation to nation.

Pathophysiology

The COPD is a debilitating lung condition produced by a variety of lesions in the large airways, bronchioles and lung parenchyma. Clinically present as inflammation of the air tubes called Bronchitis and increased mucous production resulting in airway obstruction. Histologically the obstruction is caused by activated inflammatory cells which produce bronchiolar breakdown of the structural proteins (collagen and elastin) along with cellular apoptosis, inappropriate production of Matrix Metalloproteinase-9 (MMP9) and lack of lung tissue repair function^[51,52]. In a small group of cases there is enlargement of lung spaces with fibrosis and narrowing of bronchioles resulting in emphysema.

Current treatment challenges

The current treatment options include cessation of smoking, bronchodilators, inhaled corticosteroids, pulmonary re-habitation, oxygen therapy and surgery. The β -agonists type of bronchodilators work by relaxing bronchial smooth muscle and these β -agonists have twofold increased risk of causing cardiovascular disease as adverse event^[53,54].

Mechanisms of Action of ADSCs for COPD

ADSCs showed improved regenerative and reparative function in mice with elastase-induced emphysema^[55]. Further, intravenous injection of MSCs has a greater *in-vivo* cell distribution towards lungs as 83 % of cells are present at 1 hour after injection, 42 % till 24 hours and 1 % till 10 days than all other organs (heart, liver, kidney, spleen and gut 1 %)^[56]. ADSCs treatment in COPD showed significant improvement in functional scores^[57]. Preconditioned pioglitazone ADSCs had a more potent therapeutic effect than non-pretreated ADSCs in both elastase and smoke-induced emphysema models and have shown higher VEGF levels in mouse lungs^[58]. Adiponectin enhances the functional role of epithelial and endothelial pulmonary cells^[59]. The recently published result of clinical trial results of MSCs treatment for COPD reveals that MSCs administration of 3 intravenous doses (weekly interval) of 2 million per kg body weight is safe and may improve the quality-of-life^[60]. Further large-scale conformational clinical trials are needed to evaluate efficacy.

Sclerosis based indications

The sclerosis indicates hardness due to inflammation, muscle stiffness and fibrosis. Applicability of ADSCs for some ischemic conditions namely Amyotrophic Lateral Sclerosis (ALS), Multiple Sclerosis (MS) and Systemic Sclerosis are reviewed here.

Amyotrophic Lateral Sclerosis (ALS)

ALS is a rare group of progressive neuromuscular degenerative disease of motor neuron system.

Incidences and prevalence

The estimated global annual prevalence rate was 1.9 cases per 100,000 with lowest rates among African and Asian populations^[60]. ALS is projected to increase at the rate of 69% from 2015 to 2040 and is mainly due to aging population^[61].

Pathophysiology

The various genetic abnormalities in chromosome 9 of C9ORF72 gene, SOD1, TDP-43, FUS/LTS, VCP/97 can cause ALS^[62-64]. The ALS is identified by degenerative changes in lower and upper motor neurons with progressive muscle atrophy, weakness typically leading to respiratory failure and death^[65,66].

Current treatment challenges

The Riluzole (Rilutek) is only the USFDA approved disease modifying drug believed to reduce the motor neuron damage by decreasing the transport messenger glutamate between nerve cells and motor neurons. Currently several mechanisms are being explored to select novel therapeutic candidate for ALS using mouse model^[67]. Majority of the pharmaceutical active substances are uni-functional and are in preclinical testing.

Mechanisms of Action of ADSCs for ALS

The therapeutic application of ADSCs to treat ALS is by direct cell replacement, trophic factor delivery, immunomodulation^[68]. ADSCs administration to SOD1-mutant mice delayed the motor neuron degeneration for 4-6 weeks and promoted neuroprotection and prolonged the lifespan^[69,70]. Autologous

ADSCs administered intrathecally in Phase-I trials were proven safe and provided Class IV evidence for dose escalation in ALS patients^[71]. Cells from ALS patients has reduced or altered therapeutic effects^[72-75]. This problem may be overcome with the use of allogeneic cells. Several ongoing clinical trials are exploring the intramuscular delivery route and optimizing the cell doses for effective treatment. Exosomal based therapeutic strategy from ADSCs, ADSC conditioned media, Curcumin-INVITE micelles loaded MSCs are some of the advanced therapeutic strategies which have shown promising pre-clinical outcome^[76-79]. The comparative study of disease modifying agent Riluzole with cell-therapeutics along with spike in *in-vitro* and *in-vivo* studies provide an opportunity to develop proof-of-concept for cell based therapies.

Multiple Sclerosis (MS)

Multiple Sclerosis is a chronic inflammatory, and autoimmune disease caused by the demyelination of nerve cells in the brain and spinal cord leading to irreversible damage to the central nervous system (CNS)^[80].

Incidences

The prevalence of MS is high as 100 / 100,000 in North America and Europe and low as 2 / 100,000 population in Eastern Asia and Sub-Saharan Africa^[81]. The most common type (85 %) of MS is Relapsing-remitting (RPMS) and other categories are secondary progressive, primary progressive, and progressive relapsing^[82].

Pathophysiology

MS is a self-directed autoimmune reaction to myelin antigen, causing irreversible damage to the myelin sheath, oligodendrocytes, axons and neurons. This causes neurological disabilities like visual disturbances, muscle weakness, trouble with coordination and balance, bowel and bladder incontinence etc^[83].

Current treatment challenges

Current treatment modalities include immunosuppressive drugs like cyclosporine, Rapamycin for the inhibition of IL-2 transcription, mAbs like anti-CD4 for depletion of T-cells, anti-CD20 (Rituximab) for depletion of B-Cells. The drugs like anti-CD2, anti-CD45, anti-CD154 (CD40L) Natalizumab etc, block the entry of inflammatory cells into the Central Nervous System. Lastly Anti-Histamines, Statins etc alter the immune response in CNS. Unfortunately, these therapies have a moderate success rate of 30 % in reducing the symptoms and most of these therapies are unable to stop the progression of disease^[84]. Besides, these drugs induce several side effects that limit its usage for an extended period^[85].

Mechanisms of Action of ADSCs for MS

Advances in understanding the pathophysiology of MS endorses the development of ADSCs based therapeutic approaches^[86]. The initial inflammatory phase occurs in the majority of cases (85 - 90 %) in RRMS. ADSCs can stimulate local specific immunomodulation, provide neuroprotection repair, and regeneration with the help of trophic factors. Transplantation of ADSCs reduces the inflammatory cell infiltration, demy-

elination and improves the neurological functions in encephalomyelitis (EAE) mice^[87]. ADSCs transduction with the Interferon beta gene in EAE model of mice (ideal model for MS) showed decreased peripheral and central neuroinflammation^[88]. IL-4 overexpressing ADSCs are potent anti-inflammatory agents in animal models^[89]. Non-transduced ADSCs from obese donors showed reduced efficacy in EAE model suggesting donor demographics and qualification criteria are important for potency of therapeutic ADSCs^[90]. Cell therapy for MS are feasible and safe, however the ADSCs based clinical trials needs to be built based on pre-clinical data as well as upgrading advanced cell delivery strategies^[80].

Systemic Sclerosis

Systemic Sclerosis (SSc) is a rare complex chronic systemic autoimmune disorder affecting blood vessels, and connective tissue.

Incidences and prevalence

SSc affect about 2.5 million worldwide and more likely to affect women than men^[91]. The under estimated annual incidence was around 20 per million population and reasonable estimate was around 500 per million population^[92]. Incidences and prevalence of SSc are higher in European nations compared to Asian nations^[91]. The overall 10 year survival after diagnosis is below 70 %.

Pathophysiology

SSc is characterized by progressive fibrosis of the skin and visceral organs due to accumulation of collagen and Extracellular Matrix (ECM), systemic inflammation due to the generation of autoantibodies and pro-inflammatory cytokines and microvascular abnormalities^[91]. The localized form of scleroderma / SSc are limited to skin, face hands and feets, but the systemic/diffuse form involves visceral organs. SSc based organ complications include Raynaud's Phenomenon (RP), Pulmonary Arterial Hypertension (PAH), scleroderma renal crisis, gastrointestinal, skin and Digital Ulcers (DUs).

Current treatment challenges

Treatment modality include corticosteroids, and Immunosuppressants. Nonsteroidal anti-inflammatory drugs alleviate the symptoms and do not slow down the progression of disease. Short-term usage of steroids has side effects like hyperglycemia, neuropsychological effects and its long term usage might cause osteoporosis, aseptic joint necrosis etc^[93]. The monoclonal antibodies for PDGF/TGFβ1 and therapeutic molecules like Tyrosinkinase inhibitors, relaxin are well tolerated therapies for scleroderma, but lacks significant efficacy^[94]. Autologous fat grafting has become a first choice to treat cutaneous lesions. Though, lipoaspirate and fat transplantation has advanced and attained attractive procedure for various reconstructions, it's still associated with increased number of complications^[95]. Typical complications includes minimal / no graft retention, oil cysts, calcification, infection, necrosis of grafted fat and surgery related complications^[95]. Major disadvantage of fat harvesting is the requirement of large volume (about 300 to 600 ml) and subsequent transplantation which may not be easy in thin patients.

Mechanisms of Action of ADSCs for SSC

ADSCs exhibit immunomodulatory properties, suppression of collagen reactive T cells and anti-inflammatory properties^[96]. The co-transplantation of autologous ADSCs along with hyaluronic acid has demonstrated a significant improvement without any complications in scleroderma patients^[97]. Allogeneic ADSCs showed anti-fibrosis effects in hypochlorous acid (HOCl)-induced mouse model of SSc crossing species barrier^[98]. Safety and efficacy using SVF injections for systemic sclerosis further strengthen the application of ADSCs^[99]. However processed SVF in IVD degeneration animal model showed destructive responses. These adverse event either be model specific or species specific triggers a caution for autologous SVF injections^[100]. ADSCs should be considered for future clinical trials, as it is a promising therapeutic candidate for SSc.

Crohn's based fistula

Crohn's Disease (CD) is rapidly evolving chronic inflammatory digestive track disease that may affect anypart of gastro-intestinal tract from mouth to anus. Perianal fistula is a well-known complication of the Crohn's disease.

Incidences and prevalence

Perianal fistula is a well known complication of CD and prevalence of a fistula-in-ano range from 1.1 to 2.2 per 10,000 population per year^[101,102]. An increase of 4% year on year was reported. It was more prevalent in males than females (24:1) with grade 4 as a common type of fistula in India^[103,104]. The unknown aetiology of complex perianal fistula results in origin of few hypothesis like deep penetration of ulcer; derivation from an anal gland abscess^[105].

Pathophysiology

The epithelial cell defects and inflammation causes leukocyte recruitment leading to altered repair mechanism that enhances the migration of intestinal epithelial cells (IEC)^[106]. The inflammatory cytokines-like TGF-β, TNF-α, and IL-13 induces IEC to myofibroblasts via EMT pathway and become transitional cells of fistula tract^[107]. This creating the transitional cell invasiveness leading to cascading events of over activation of Matrix Metalloproteinases (MMP) like MMP-3 and MMP-9 contributing to the development of fistulas^[107].

Current treatment challenges

Various treatments modulates such as antibiotics, immunomodulatory agent anti-TNF α, surgical interventions, fibrin glue and plug have been tried with varying degree of success. Use of antibiotics resulted in incomplete closure of fistula^[108]. The closure rate with the anti-TNF-α antibodies are also unsatisfactory^[109,110]. The shutdown of inflammatory response increases the risk of infections and malignancy^[111]. The outcome of medical treatment with surgical management does not sufficiently improve the quality-of-life^[112,113]. While most acute cases can be easily treated through surgery, treatment of complex perianal fistula is a formidable challenge for most surgeons^[114-116]. Aggressive, repeated surgery results in fecal incontinence, intraoperative difficulties and limited surgical management leads to recurrence^[117-119]. Fibrin glue while preserving anal sphincter function results in a clinical efficacy of about 38 % and needs

long-term follow-up^[120]. The reported success rate of Fistula plug made of porcine small intestinal submucosa called from Cook Biotech in non-CD and CD fistulas were 54.8 and 54.3 % respectively^[121]. Hence there is a need for better regenerative products for the better clinical outcome.

Mechanisms of Action of ADSCs for Fistula

The anti-inflammatory, self-renewing, and differentiation property of ADSCs might play a critical role in the healing of anal fistulas. First successful clinical evidence of the effectiveness of ADSCs in rectovaginal fistula of CD was reported as a case study^[122]. Symptoms did not improve for 11 years prior to enrolment, but the fistula was completely closed within one week after infusion of ADSCs at the site^[122]. Thereafter several clinical trials were initiated across the globe for fistula. The SVF offers instant therapeutic materials for infusion or injection, but clinically, expanded ADSCs are more effective than SVF^[123].

In Phase I trials application of Autologous ADSCs resulted in complete fistula closure in 75 % of cases by 8th week^[124] and healing rate of 71 % by ADSCs and 16 % by placebo in Phase II trials by the same group^[125]. Infusion of autologous ADSCs achieved fistula healing and remission in 88 % of cases at 1 year^[126]. Long-term follow-up at 3 years demonstrated that the administration of ADSCs were safe and efficacious with no reoccurrence in fistula^[127]. Phase II study with allogeneic ADSCs reported a 85.7% healing rate with ADSCs compared to 33.3% healing rate with placebo^[128]. In addition, García-Arranz M et al., (2015) demonstrated the ADSCs safety and efficacy in phase-I-IIa by administration of 20 million ADSCs through intra-lesional injection and second dose of 40 million at 12 week to unhealed fistula by following the patients upto 52 weeks^[129]. Phase-III randomized double-blinded controlled trials using allogeneic ADSCs by TiGenix have shown safe and effective clinical outcome^[130]. Based on these results, TiGenix applied for European Medicines Agency for approval of the treatment^[131]. Gastroenterology based pharmaceutical leader of Takeda acquired the exclusive rights to commercialize the product outside the US. None of the clinical trials reported major adverse reactions. Currently, 21 of academic and 11 of industry-sponsored clinical trials on fistula with various combinations of cell delivery options are underway. The recent meta-analysis also support the therapeutic effects of MSCs on Crohn's fistula^[132]. Biodistribution studies of ADSCs using bioluminescence in animal model demonstrate a correlation between more viable ADSCs on day 30 in fistula and healing rate^[133]. The pre-clinical, clinical trial exploration, commercialization and further conceptual development in fistula indication suggest that ADSCs may be the possible alternative treatment, but confirmatory evidence-based long-term follow-up studies are required on a large population.

Osteoarthritis

Osteoarthritis (OA) is a degenerative joint disease characterized by progressive cartilage deterioration, subchondral bone alteration, osteophyte formation, and loss of joint space^[134].

Incidence and prevalence

OA is the leading cause of disability in the elderly and affects approximately 10 % of those aged over 60 years^[135]. OA incidence is rising due to increasing obesity and an ageing popu-

lation^[134-136]. OA is the fastest increasing major health condition. Between 2005 and 2015, there was a 32.9 % increase in prevalence and 34.8 % increase in years lived with disability^[137].

Pathophysiology

OA also affects joint capsule, meniscus and the synovium^[138-142]. In OA pro-inflammatory and catabolic cytokines are produced leading to cartilage degradation^[142] which further induces inflammation leading to a vicious cycle of further cartilage degradation and inflammation. The clinical symptoms of OA are persistent joint pain, stiffness disability and loss of joint function^[143-146].

Current treatment options

The current non-surgical treatment options including physical therapy, opioids, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and lubricating supplements. Physical therapy can improve joint function and can provide pain relief but cannot regenerate cartilage^[144,147]. The pain relief is often not enough^[148-150]. Opioids provide small to moderate benefit but are associated with adverse events such as cardiovascular events, fractures, addiction^[151-153]. While NSAIDs suppress inflammation and provide pain relief, its therapeutic benefits are only palliative and do little to treat and prevent cartilage damage^[147]. NSAIDs are associated with an increased risk of serious Gastrointestinal (GI), Cardiovascular (CV), renal injury, and liver damage^[154-161]. Intra-articular corticosteroids can provide short-term relief from pain but repeated injections might lead to joint damage and increase the infection risk^[144]. Lubricating substances such as hyaluronic injections can provide pain relief and improved joint function^[161], but show varying efficacy^[144,162].

Mechanisms of Action of ADSCs for OA

ADSCs can help in treating OA, primarily through the paracrine effects of the secretory factors which attenuates the inflammation, imparts chondroinductive and chondroprotective effects. ADSCs attenuate inflammation by lowering the production of catabolic and inflammatory factor^[163-165]. Thus by targeting the inflammatory process and the catabolic factors ADSCs can break the progressive loop of OA and prevent the progression of cartilage degradation. ADSCs have the chondroinductive effect on chondrocytes, by promoting the expression of cartilage specific markers^[166,167], by reducing the expression of hypertrophic chondrocytes markers and fibrotic markers^[168]. ADSCs also provides chondroprotective effect by promoting chondrocyte proliferation and by reversing apoptosis^[165,168]. ADSCs may be able to affect OA by directly differentiating into chondrocytes. Various *in-vitro* studies demonstrate ADSCs differentiation into chondrocytes. However some *in-vivo* studies show that ADSCs home to the synovium and not to the cartilage^[164,165]. Hence the contribution of ADSCs in OA could be due to the inhibition of cartilage degeneration and might not be through ADSC differentiation into chondrocytes.

The beneficial effects of ADSCs on OA have been demonstrated in various OA induced animal models such as rabbit^[139,169], dog^[170-173], goat^[174], mouse^[175], horse^[176], rat^[177]. ADSCs have been administrated along with serum^[139,167], hyaluronic acid^[170,177], medium^[169], PBS^[171,176,177], PRP^[173]. Efficacy was demonstrated when the cells were of autologous^[171-173], al-

logeneic^[170-172] or xenogeneic^[171]. Various joints were used such as hip^[171], elbow^[170,172], knee^[167,175-177], humero radial joints^[173], middle carpal joint^[176]. There are only a few clinical cases published on the use of ADSCs. Various dosages (Low-dose (1.0×10^7 cells), medium mid-dose (5.0×10^7 cells), and high-dose (1.0×10^8 cells) of autologous ADSCs in saline were injected in patients with knee OA. The high dose group demonstrated both pain improvement and increased volume of hyaline like cartilage at 6 months^[178]. These clinical outcomes tended to deteriorate after 1 year in the low- and medium-dose groups, whereas those in the high-dose group plateaued at 2 years^[179]. In another dose escalation study with three doses (low-dose (2×10^6 cells), medium mid-dose (10×10^6), and high-dose (50×10^6) lower dose of autologous ADSCs improved pain and knee function at 6 months in 18 patients^[180].

Cell Therapies for OA

In the absence of disease modifying agents, cell-based therapies that regenerate cartilage is ideal for OA. There are a few approved cell-based therapies and more are in various stage of clinical trials. Carticel and MACI from Genzyme approved by the FDA and Chondrocelect approved by European Medicines Agency use autologous chondrocytes. CARTISTEM®, approved by Korean FDA use human umbilical cord blood-derived mesenchymal stem cells in sodium hyaluronate. Other products such as Chondrogen® MSC in HA from Osiris Therapeutics (NCT00225095, NCT00702741), BioCart® scaffold containing autologous chondrocytes from ProChon Biotech (NCT00729716), Mesoblast allogeneic mesenchymal precursor cells in Rheumatoid Arthritis (NCT01851070), Progenza Allogeneic ADSCs from Regeneus (ACTRN12615000439549), and Neocart autologous chondrocytes in collagen matrix from HistoGenics (NCT01066702, NCT00548119) are in various stages of clinical trials.

Overall these few clinical studies demonstrate that ADSCs are capable of reducing pain and improving functions in OA. More randomized controlled trials are needed before ADSCs can come to the clinic.

Clinical Translational Challenges for ADSCs

The ADSCs are fascinating tools for regenerative medicine and its clinical translation exploration for various indications encounter ethical, non-specific/specific regulatory and legal framework challenges. ADSCs therapies are hampered by long development duration and undergo lengthy clinical phases execution to reach the market because of current regulatory framework^[181,182]. ADSCs clinical translation can be accelerated up by adopting translational modalities and basic quality framework from bone marrow and blood transfusion methodologies^[183]. Further, risk-based classification of regenerative therapeutics of Japanese regulatory model which heralded new reforms, enabling new outlook to regulatory translations ensuring the patient safety and clinical research can also speed up the translation^[184]. The need of the hour is for tailor made regulations based on product classification, with minimal regulatory intervention in initial stages of clinical development to ensure proper development of product, procedures and its real-time cold chain logistics.

Conclusion

ADSCs as a therapeutic agent has several advantages over drugs in many clinical indications. Recent progress of ADSCs towards various clinical trials suggest its usability as core active therapeutic by tapping its natural abilities of anti-inflammation, repair, regeneration and immunomodulation properties. ADSCs have been shown to slowdown the disease progression and can be tested as a potential therapy for incurable diseases. This review focusses on the scientific evidence of using ADSCs for some clinical indications. Current regulations delay the clinical translation of ADSCs. The Japanese risk-based regulatory approaches^[184] on stem cells can provide a path to develop regulatory framework to speed up the release of ADSCs based product to market with uncompromised safety and quality.

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Authors' Contributions

Dr. Sanjay Gottipamula: The first author made a significant contribution to conception and design, administrative support, provision of study materials, search, navigation, data collection and assembly of data, data analysis and interpretation, drafting and revising the manuscript.

Dr. Kumar Chokalingam: The second author made significant contribution in research navigation, data collection, interpretation and drafting of the manuscript.

Dr. K.N Sridhar: Corresponding author of the article and made a significant contribution in revising, provision of study materials and final approval of the manuscript.

Conflict of Interest

The author discloses no conflict of Interest.

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