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A REVIEW ON "THERAPEUTIC POTENTIAL OF REGENERATIVE MEDICINE: AS A TREATMENT FOR THE AUTOIMMUNE DISEASES"

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ABSTRACT

Autoimmune diseases are conditions in which the patient's immune system generates cellular and antibody responses to substances and tissues normally present in the body. This might be restricted to one organ or involve a particular tissue in different places. As a result of this immune response, damage to different organs occurs. Currently, autoimmune conditions are treated with immune suppressive agents such as steroids, methotrexate, cyclosporine, gold, and more recently infliximab. Despite inducing temporary improvement, these approaches possess the possibility of long-term adverse effects, as well as need for life-long treatment. Stem cells have the unique ability to modulate the immune system so as to shut off pathological responses while preserving its ability to fight off disease. Mesenchymal stem cells (MSCs) are now known to display not only stem cell multipotency, but also robust anti-inflammatory and regenerative properties. After widespread in-vitro and in-vivo preclinical testing, autologous and allogenic MSCs have been applied in a range of autoimmune conditions; Graft versus host disease (GvHD), Crohn's disease, multiple sclerosis, refractory systemic lupus erythematosus and systemic sclerosis.

***Keywords*:** Autoimmune disease, Stem cells, Mesenchymal stem cells, Regenerative Properties

INTRODUCTION

Autoimmune disease [AID also called as autoimmune disorder] is a result of immunological imbalance and intolerance. In such a condition, an immune response is produced against the healthy tissues or substances present in our own body. [1] A series of events trigger AID, but the trigger that causes such a holocaust still remains unknown. Environmental factors, mis-regulation of immune system, and heredities are few common factors that influence AID out of the humungous list. Smoking, alcohol, industrial pollution, oral contraceptives, birth weight, protein intake, geography, and socioeconomic status are some of the possible environmental triggers associated with AID. In case of mis-regulation of genes, the association of human leucocyte antigen (HLA) class II encoded HLA-DRB_1-DQA_1-DQB_1 haplotype has been detected with several AIDs, including type 1 diabetes, Graves' disease, and rheumatoid arthritis.[2] MSCs were able to suppress inflammation and reduce damage to the kidneys and bowel through the possible induction of regulatory T cells in patients. It also has been reported that BM-MSCs can improve multiple system atrophy (MSA), amyotrophic lateral sclerosis (ALS), and stroke. [3]

GRAFT VERSUS HOST DISEASE (GVHD)

GVHD is a major cause of morbidity and mortality after allogeneic hematopoietic stem cell transplant or donor lymphocyte infusion. This can occur in up to 30–50% of patients despite HLA- matched sibling transplant and even more frequently in HLA-mismatched unrelated donor transplants (60–80%). Corticosteroids remain the first-line treatment; however, despite the addition of other steroid sparing agents such as calcineurin inhibitors, prognosis for steroid-refractory aGVHD patients remains poor with 5-year survival of less than 30%. Furthermore, many patients may either progress from aGVHD or develop de novo chronic GVHD (cGVHD) with similar high risk of morbidity and mortality. MSCs have been examined for use both in the prevention and treatment of acute and chronic GVHD. [4]

MSCs in the Treatment of Graft-versus-Host Disease

Multiple early phase studies have explored the feasibility of different methods of MSC manufacturing and delivery. While phase II studies suggest clinical efficacy of this modality, two large, multicenter, prospective phase III trials have examined the use of MSCs to treat de novo aGVHD and therapy-refractory acute and chronic GVHD without evidence of efficacy as determined by the primary endpoints. Better understanding of the mechanism of action of this cell therapy modality is needed to optimize therapy and identify the GVHD population that may benefit from this treatment. The largest clinical experience has been with IV infusion of MSC cultured from bone marrow-aspirate in fetal bovine serum.[5]

Some important factors have helped ease the transition to commercialize the manufacturing process of this treatment modality. First, the finding of comparable efficacy and lack of toxicity in MSCs from HLA-mismatched unrelated donors allows the use of pre-manufactured,

cryopreserved MSCs from a larger donor source, thereby removing the time constraint and increasing the accessibility of MSCs. Second, commercially available, quality-controlled culture media and supplement can help minimize some of the inter sample variability in the culture process.

The concern for increased risk of disease relapse and infection due to the immunosuppressive properties of MSCs cannot be adequately addressed with the existing data. Heterogeneous patient populations were enrolled across these studies with limited controls for comparison. Many enrolled patients are at inherently at high risk for disease recurrence and infection due to the nature of their disease and treatment. This is a valid concern that will need to be carefully analyzed in randomized, placebo-controlled phase III studies. The dose and frequency of MSCs infusion to maximize clinical efficacy has not been addressed in these smaller studies. While the technical limitations from manufacturing have improved to allow for infusion in the range of 10^6 cells/kg, the biokinetics of the infused MSCs is poorly understood. A better understanding of the underlying biology is needed to rationally design further phase III trials attempting to confirm efficacy and clarify risk of disease relapse and infection. Optimization of MSCs therapy in GVHD and other clinical conditions will require better understanding of these cells' mechanism of action and how these functions are affected by other existing treatment modalities. This knowledge can then be translated to improve the design of MSCs therapy. Advances in personalized medicine should be employed to identify the patient population likely to benefit from MSCs therapy and the role of MSCs in combination with existing treatment modalities.[6]

Ulcerative Colitis (UC) and Crohn's Disease

Ulcerative colitis and Crohn's disease are the principal forms of inflammatory bowel disease. Both represent chronic inflammation of the gastrointestinal tract, which displays heterogeneity in inflammatory and symptomatic burden between patients and within individuals over time. In the past decade there have been major advances in investigations, pharmacological, non-pharmacological and surgical interventions for both UC and Crohn's disease.[7]

UC is characterized by mucosal inflammation starting distally in the rectum, with continuous extension proximally for a variable distance, often with an abrupt demarcation between inflamed and non-in- flamed mucosa. Typically, patients with UC experience periods of relapse and remission. Up to 90% will have one or more relapses after the first attack, and early relapse or active disease in the first 2 years is associated with a worse disease course subsequently. In patients presenting with suspected UC, stool cultures and Clostridium difficile toxin assay should always be performed to rule out infective causes. While UC is often initially diagnosed at flexible (or rigid) sigmoidoscopy, it is important to confirm the diagnosis, extent and severity of disease by means of full ileocolonoscopy, usually within the first year, as this can more definitively confirm

the diagnosis of UC versus Crohn's disease and give information that may help to predict future disease course, including potential and risk stratification for dysplasia, and thus will influence treatment choices.[8]

Rectal sparing in UC has been described in up to >3% of patients, but more frequently patchy inflammation of the rectum may be seen in those who have been given empirical topical therapy.[9] The presence of a 'caecal patch', isolated peri-appendiceal inflammation and backwash ileitis can occur in UC, but if the histology and clinical pattern are not otherwise typical of UC, then small bowel evaluation is required to exclude Crohn's disease (see Section 4.1.3.1: Crohn's disease, Cross-sectional imaging: CT, MR and small bowel ultrasound). Backwash ileitis has been reported in up to 20% of patients with extensive colitits. No histological feature is diagnostic of UC, but the combination of basal plasmacytosis, diffuse crypt atrophy and distortion, villous surface irregularity and mucus depletion are suggestive of a diagnosis of UC in the correct clinical context.[10] Uneven distribution of inflammation within the colon or within biopsies can occur in patients with long-standing disease, or after treatment.

In 5–15% of IBD patients, endoscopic and histological assessments cannot distinguish between Crohn's colitis and UC, and these patients are labelled as IBD-unclassified (IBD-U), or if features are still indeterminate after colectomy histology is assessed, described as indeterminate colitis. IBD-U is more common in children than adults. In a small proportion of UC patients their diagnosis is later changed to IBD-U or Crohn's disease.[11]

Management of UC and Crohn's disease

The ultimate target of medical therapy is a contentious issue as there is no fully agreed or validated definition of remission, although many parameters have been suggested both clinically and endoscopically. Using mucosal healing as a treatment target is contentious because of the implications for clinical practice, with the need for more endoscopic assessment and likely escalation of therapy in asymptomatic patients. In an Australian retrospective study, 61% of 246 patients were in clinical remission, but only 35% were in both clinical and endoscopic remission (Mayo endoscopic sub score ≤1), and only 16% of the 246 patients were also in histological remission. Using the Mayo endoscopic sub score, there is no consensus on the value of achieving a score of 0 rather than 1, with documented differences in future disease course between the two. There is lack of clear evidence about the importance of histological remission as well as endoscopic remission. Oral 5-ASA (5-aminosalicylic acid) is the standard therapy for mild to moderately active UC. Meta-analyses support the efficacy of oral 5-ASA for induction therapy for mild to moderately active UC. [12] [13] Once daily dosing is as effective as divided doses. Doses ≥2 g/day are more effective than dosages <2 g/ day for remission (RR 0.91; 95% CI 0.85 to 0.98).[14] The majority of patients with mild to moderate UC will respond to 2–3 g 5-ASA (depending on formulation used) and higher doses can be

used in those with more severe symptoms or those not responding initially. Prednisolone is superior to 5-ASA for induction of remission in UC, but has significant side effects and should be reserved for patients with failure of response or who are intolerant to oral and/or rectal 5-ASA.[15] [16]

Crohn's disease is a complex chronic inflammatory gastro-intestinal condition with variable age of onset, disease location and behavior. There is no single unifying definition of Crohn's disease and a combination of investigative modalities is often needed to confirm the diagnosis. The most widely accepted framework for making a diagnosis dates back nearly 30 years. [17] Factors include an appropriate clinical history and examination, ileocolonoscopy, small bowel imaging, blood tests and histology. Mucosal biopsies from endoscopic procedures or surgical resection specimens show focal or patchy (rather than diffuse) inflammation and/or crypt distortion. Discontinuous segments of disease ('skip lesions'), ileal involvement and granulomatous inflammation are more suggestive of Crohn's disease, as is a tendency for inflammation to be worse in the proximal colon. Partially-treated UC can demonstrate patches of inflammation, backwash ileitis occur in UC, and granulomas only occur in about half of Crohn's disease patients. Cryptolytic granulomas can occur in UC, diverticular inflammation and all forms of colitis and are very non-specific. Studies have shown about 3% of UC patients will be reclassified as Crohn's colitis, and conversely a small number (0.6–3%) will be reclassified to UC after an initial diagnosis of Crohn's disease.[18] [19]

The Crohn's disease activity index (CDAI) has in the past been used in clinical trials, but it has a number of limitations, including the parameters used to define remission (CDAI<150), and contemporary trial design no longer favors use of CDAI. In clinical practice, CDAI is cumbersome to calculate, requires diary data from patients, is weighted towards diarrhea (which is often caused by factors other than inflammation), is not usable in patients with stomas and is not validated for use after surgery.[20] In mild, moderate and severe colonic Crohn's disease, systemic corticosteroids such as prednisolone are effective in inducing remission. A starting dose of 40 mg tapering by 5 mg weekly is often used, but should be tailored to disease severity and patient tolerance. Ileal-release budesonide does have benefit in Crohn's disease affecting the proximal colon, but there is no evidence of benefit in more distal colonic inflammation. There are no trials of colonic-release budesonide-MMX in Crohn's disease at present. Meta-analysis has shown that EEN is as effective as corticosteroids at inducing remission in 73% of Paediatric patients on an intention to treat basis but not in adults. In pediatrics, it is considered the primary treatment option to induce disease remission, and has added value in that it not only improves nutritional status but also benefits growth. [21] In adults, although studies have been small and underpowered, there does seem to be a consistent message that, where tolerated, EEN can be effective at

inducing remission even in the presence of complications. There is increasing evidence that EEN can alter the microbiome, with differences in those who have a long-term response. Antibiotic therapy in Crohn's disease has studied a wide range of antimicrobial agents. While a meta-analysis demonstrated efficacy for these pooled trials over placebo (RR for continued disease activity 0.85 (95% CI 0.73 to 0.99), p=0.03), there was such heterogeneity in the agents and dosing regimens used that it makes it difficult to draw meaningful conclusions. The risk of adverse effects, particularly with prolonged or repeated courses, should also be taken into consideration. In this regard, Rifaximin (a non-absorbed oral antibiotic), in an extended-intestinal release formulation has been shown in a large dose-ranging study to be effective.[22]

Relapse of Crohn's disease is common on corticosteroid withdrawal, particularly in moderate to severe disease, and early initiation of corticosteroid-sparing therapy is appropriate. Immunomodulators such as azathioprine, mercaptopurine or methotrexate are effective in the maintenance of remission of Crohn's disease. Thiopurines should not be used for induction of remission in active Crohn's disease. Thiopurines are more effective than placebo in maintenance of remission in Crohn's disease but the Cochrane analysis reports low quality evidence (NNT=9). A systematic review and network meta-analysis also showed the benefit of azathioprine/mercaptopurine compared with placebo in remission maintenance (OR 1.7 (95% CI 1.3 to 2.6)), although anti-TNF therapy was significantly more effective than thiopurines.[23] Methotrexate should not be used as monotherapy for induction of remission, but may be used in Crohn's disease patients failing to respond to corticosteroids. The landmark trial evaluated intramuscular methotrexate 25 mg weekly given to patients with chronic active Crohn's disease despite at least 3 months of prednisolone. It showed increased clinical remission rates compared with placebo at 16 weeks, with reduced prednisolone requirements. UK data from 1990 to 2010 show over half of patients with Crohn's disease were prescribed 5-ASA, and Swiss data show it is more often given for Crohn's colitis.[24] A Cochrane system- atic literature review showed that oral 5-ASA has no efficacy in maintaining clinical remission in Crohn's disease, with similar negative findings in meta-analyses for induction or maintenance. A recent review of colonic Crohn's disease showed that there was no benefit for 5-ASA in colonic Crohn's disease, but two studies have shown possible benefit for sulphasalazine in remission induction. Thus, 5-ASAs are not recommended for induction or maintenance treatment of Crohn's disease.[25] Adalimumab is a monoclonal antibody to TNF administered subcutaneously. The CLASSIC I study in moderate to severe Crohn's disease naïve to anti-TNF therapy showed that the optimum dose for induction therapy was 160 mg followed by 80 mg at week 2, with remission (CDAI <150) achieved in 36% (p=0.001 against placebo) compared with

24% (80 mg/40 mg), 18% (40 mg/20 mg) and 12% on placebo. There is little to choose between adalimumab and infliximab in efficacy in luminal Crohn's disease, and practical considerations regarding mode and frequency of administration are the main factors as well as consideration of the relative need for combination therapy with an immunomodulator. Vedolizumab is a monoclonal antibody to the integrin and blocks lymphocyte trafficking to the gut by blocking the binding of to the mucosal address in cell adhesion mole- cule-1 (MAdCAM-1). Ustekinumab is an anti-IL12/23 p40 antibody and has been evaluated in the UNITI and IM-UNITI studies in patients with Crohn's disease.[26]

Hematopoietic stem cell transplantation

Despite the increasing range of drugs available, there are still a number of Crohn's disease patients with severe resistant disease or in whom surgical resection is not appropriate (usually due to extensive disease or incipient short bowel syndrome). For this group of patients, autologous hematopoietic stem cell trans-plantation (HSTC) has been used. The ASTIC study, an RCT of autologous HSTC published in 2015, set a high bar for its primary end point (of sustained therapy-free clinical, endoscopic and radiological remission at 1 year) and failed to achieve it. One of the 23 patients undergoing HSTC died and serious adverse events (particularly infection) were common, especially in individuals with perianal Crohn's disease. Nonetheless in this treatment-refractory population there were, among the component parts of the composite primary outcome, suggestions of benefit in some patients and further trial data are needed.[27]

Refractory Systemic Lupus Erytgematosus

Systemic lupus erythematous (SLE) is an auto-immune inflammatory disease with multi-organ involvement including the kidney, brain, lung and hematopoietic systems. Lupus nephritis (LN) is a common major organ manifestation and is a significant cause of morbidity and mortality. The most widely and classically used immunosuppressive therapies, notably corticosteroids and cyclophosphamide (CYC), have led to a significant improvement in survival over the last few decades and decreased the progression to end-stage multi-organ failure. Both agents, however, are associated with significant side effects including increased susceptibility to infection. Currently, haematopoietic stem cell (HSC) transplantation is used in some cases of refractory SLE, which results in disease improvement in most cases, but also causes significant morbidity and mortality. The most common complications, including mucositis, transplantation-related infection and lung injury, have led to concerns regarding widespread use of this procedure in lupus. Given these current treatment limitations, new therapies are needed with enhanced efficacy and less toxicity than current treatment standards can control disease in most, but not all, patients with lupus nephritis. There is a subset of lupus nephritis patients whose disease either does not respond or relapses despite continuing

chemotherapy, and their prognosis remains poor.

MSCs are widely studied as an alternative cell source for their ability to differentiate into multiple Mesenchymal lineages, including bone, fat, and cartilage. Recent studies have indicated that these pluripotent cells also differentiate into endoderm and neuroectoderm lineages, including neurons, hepatocytes, and cardiocytes. An important function of MSCs for autoimmune diseases is their immunomodulatory effect on various activated lymphoid cells, such as T cells, B cells, natural killer cells, and dendritic cells.[28] [29] MSCs express low levels of HLA class I major histocompatibility complex (MHC) molecules and are negative for class II MHC costimulatory molecules such as CD80, CD86, and CD40. MSCs directly suppress activated T cell proliferation in an antigen-independent and dose-dependent manner. These characteristics support the possibility of using MSCs for therapeutic applications in autoimmune diseases.

Multiple System Atrophy (MSA)

MSA is a rapidly progressive sporadic adult-onset neurodegenerative disorder. It was first termed to describe neuronal atrophy found in various diseases, including striatonigral degeneration, olivoponto cerebellar atrophy, and Shy-Drager syndrome**.** MSA is characterized by clinical symptoms that are subdivided into extrapyramidal, pyramidal, cerebellar, and autonomic symptoms**.** The autonomic symptoms include common autonomic dysfunctions, such as urogenital, gastrointestinal, and cardiovascular failure. Non motor symptoms, such as sleep and cognitive disorders, respiratory problems, and emotional/behavioral symptoms, might also occur during disease development**.** The different symptoms of MSA can be used to categorize the disease into two subtypes: the parkinsonian subtype (MSA-P) and the cerebellar type (MSA-C). MSA is pathologically distinguished by a widespread neuronal loss that is accompanied by gliosis in the basal ganglia, cerebellum, pons, inferior olivary nuclei, and spinal cord.

Multiple system atrophy and glial cytoplasmic inclusions

The important neuro-pathological hallmark of MSA is the presence of argyrophilic filamentous glial cytoplasmic inclusions (GCIs), predominantly in oligodendrocytes. GCIs are spherical protein aggregates located near nuclei with a diameter of 5–20 μm and various morphologies. GCIs in oligodendrocytes are usually larger and paler than nonoligodendrocyte-derived GCIs. They are primarily composed of loosely packed filaments of a-synuclein protein that is phosphorylated at residue Ser129 and ubiquitinated. Immunohistochemical studies have identified other proteins that colocalize with a-synuclein. These include p25a/TPPP (tubulin polymerization promoting protein), a, β-crystallin, tau, LRRK2, cyclindependent kinase 5 (cdk5), microtubule-associated protein 5, ubiquitin, and tubulin. p25a/ TPPP have a vital role in the stabilization of microtubules, the projection of mature oligodendrocytes, and ciliary structures. The redistribution of p25a in oligodendrocytes causes an increase in

the volume of cell bodies, which is a typical characteristic of cells with GCIs. Ultimately, the presence of p25a in the cell body enhances the aggregation of a-synuclein, which may lead to oligodendroglial dysfunction and neuronal degeneration. [30] [31]

Multiple system atrophy and a-synuclein

MSA belongs to a diverse group of neurodegenerative disorders described as a-synucleinopathies, which are similar to PD and dementia with Lewy bodies (DLB). These disorders are characterized by the abnormal accumulation of a-synuclein protein aggregates. a-Synuclein is a predominantly neuronal presynaptic protein present in the brain and is expressed in other tissues at various levels. It is encoded by the SNCA gene, which is linked to PD and has also been associated with an increased risk of PD, DLB, and MSA.[32] The presence of GCIs and the excessive accumulation of a-synuclein in the oligodendrocytes are accompanied by neuronal degeneration, brain atrophy,demyelination, and mutation of nerve cells in MSA patients. The mechanisms of the accumulation of a-synuclein in oligodendrocytes are still unknown. Several hypotheses have provided possible explanations as to how GCIs form. [33]

Astrogliosis and microgliosis in MSA

The activation of astrocytes and microglia has been observed in the brains of MSA patients, as well as in those of transgenic models of MSA. Studies have revealed the potential role of the neuron-to-glia transmission of a-synuclein in glial activation in both cell and animal models. Extracellular a-synuclein leads to inflammatory responses in astrocytes and microglia. Astrogliosis is an important pathological characteristic of MSA. Treating astrocytes with extracellular a-synuclein induces ERK/MAPKK-dependent astrogliosis. Activated astrocytes can secrete cytokines, which may trigger microgliosis. Therefore, the proinflammatory function of extracellular a-synuclein in astrocytes may have a crucial role in spreading MSA neuropathology. Microglias are the primary immunophagocytic cells in the brain. An increased number of activated microglia is found in a-synucleinopathies. The injection of GCI extract into the mouse brain causes localized microgliosis, as well as astrogliosis. Toll-like receptors (TLRs), such as TLR2 and TLR4, have been shown to interact with extracellular a-synuclein in microglia. Microglia was activated by extracellular a-synuclein then secrete toxic factors that can trigger further neurodegeneration and gliosis.[34]

U-373 MG cell line and primary mixed rat glial cultures

A study conducted by Stefanova et al. showed that the overexpression of a-synuclein induced cell death in a U373 MG human glioblastoma astrocytoma cell line and primary oligodendrocytes from mixed rat glial cultures were highly prone to oxidative stress. Upon treatment with TNFa, a pro-inflammatory cytokine released by microglia in MSA, significant cytotoxic changes were observed in a-synuclein-expressing cells. This suggested that a toxic environment, along with high levels of a

synuclein in glia, might represent a severe risk for the development of MSA.

A list of the currently symptomatic treatment for MSA is given in Table below.

Current therapies

Table 1: Available symptomatic treatment for multiple system atrophy (MSA).

Feature	Current first line treatment	Alternative treatment
Parkinsonism	Levodopa up to 1 g/day if tolerated, in association with domperidone and physiotherapy	Dopamine agonist, amantadine, paroxetine (Friess *et al.* 2006)
Cerebellar ataxia	Physiotherapy	Clonazepam, baclofen
Neurogenic lower urinary tract dysfunction	If postvoid residual> 100 ml, clean intermittent catheterization If postvoid residual<100 ml, anticholinergic agents for detrusor hyperactivity, α-adrenergic antagonists for urethra hypertony	Botulinum toxin A in the detrusor muscle or the urethral sphincter, surgery options, permanent catheterization
Constipation	High fluid and fibre intake classical laxative therapy, polycarbophil, macrogel 3350	
Erectile dysfunction	Intracavernosal injection of papaverine or prostaglandin E1, sildenafil (Hussain *et al.* 2001)	Subcutaneous apomorphine injections
Rapid eye movement	Clonazepam	Temazepam, sodium oxybate, zopiclone
Sleep behavior disorder		Gabapentin, donepezil, pramipexole
Depression	Psychotherapy Selective serotonorgic reuptake inhibitors, levodopa therapy	Electroconvulsive therapy Repetitive transcranial magnetic stimulation
Cognitive Impairment	Speech therapy	
Drooling	Anticholinergic drugs	Injection of botulinum toxin into the salivary glands
Orthostatic hypotension	Nonpharmacological measures (custom fitted elastic stockings, raising the head of bed when sleeping, small meals). Midodrine from 2.5mg to 30 mg per day (wright et al 1998)	Fludrocortisone, pyridostigmine, droxidopa (mathias, 2008), antidiuretic hormone Desmopressin at bedtime, ephedrine.

Among all of the subjects included in these trials, there was minority of MSA patients: 40/171 subjects (low et al 1997), 7/25 (Wright et al 1998). In available subgroup analysis, beneficial effect on orthostatic

hypotension (OH) was reported (wright et al 1998).

Cerebellar ataxia

Physiotherapy remains the best therapeutic option for cerebellar ataxia in MSA. When intentional cerebellar tremor predominates, off-label use of low doses of clonazepam may sometimes help in our hands. Off-label use of propanolol, baclofen or amantadine have shown modest and transient efficacy in a retrospective data analysis. Buspirone (off-label) improved upper limb ataxia in an open-label trial including nine MSA-C patients.

Movement disorders

Dystonia: In a prospective trial including levodopa-naive patients with probable MSA, dystonia occurred in 46% [Boesch et al. 2002]. Botulinum toxin injection is the most commonly used treatment for focal dystonia. Although no controlled studies with any other drug are yet available, symptomatic relief with anticholinergics, amantadine, dopamine agonists, muscle relaxants or tetrabenazine has been reported in some MSA patients when used off-label [Papapetropoulos et al. 2008].

Rapid eye movement sleep behavior disorder (RBD) may be the presenting symptom of MSA [Tison et al. 1995] and is observed in 69-100% of systematic polysomnography recordings in MSA patients. Clonazepam may aggravate existing obstructive sleep apnoea, but alternative treatments are sparse. Sodium oxybate, temazepam, zopiclone, gabapentin and pramipexole were effective when used off-label in limited and uncontrolled single case reports [Anderson and Shneerson, 2009]. Donepezil, a centrally acting reversible acetylcholinesterase inhibitor, is expected to alleviate RBD (off-label use) [Ringman and Simmons, 2000], but its reported clinical efficacy is variable [Boeve et al. 2003].[35]

Neuroprotective strategies

Although recent advances in basic science have given some clues for neuroprotective strategies in MSA patients, all clinical trials failed to show any disease-modifying properties. Experimental evidence in a rodent model of MSA suggested that the antiglutamate drug riluzole may delay neuronal loss [Diguet et al. 2005]. No positive effect was noted in two prospective trials performed in MSA, using validated clinical scales and survival time as outcomes [Bensimon et al. 2009]. To test the hypothesis that minocycline inhibits microglial activation, which is supposed to contribute to the progressive cell death in MSA, a 48-week prospective study was performed in 63 MSA-P patients [Dodel et al. 2010]. Although a subgroup analysis of eight patients revealed a non-significant decrease in [11C](R)-PK11195-PET binding, a tracer of glial cells including microglia, astrocytes and infiltrating macrophages, there was no change in clinical measures of motor impairment or health-related quality of life.[35]

Deep brain stimulation

Although bilateral subthalamic stimulation may have beneficial effects in a few MSA patients [Visser-Vandewalle et al. 2003], a recent review of the literature highlights the poor efficacy of deep brain simulation (DBS) [Shih and Tarsy, 2007]. Moreover,

more than a quarter of patients died within 7 months of surgery. Owing to the limited number of reports, the poor outcome and the possibility of a harmful effect, DBS is currently not recommended in MSA [Wenning and Stefanova, 2009; Lambrecq et al. 2008; Shih and Tarsy, 2007; Santens et al. 2006; Talmant et al. 2006; Tarsy et al. 2003].

Future therapies

Neuroprotective strategies; although the exact mechanisms of the neurodegenerative process in MSA remain unclear, the aggregation of alpha-synuclein in oligodendrocytes has been identified as a critical step in the pathogenesis [Jellinger and Lantos, 2010; Ubhi et al. 2010; Stefanova et al. 2009; Wenning et al. 2008]. Based on the key role of alpha-synuclein aggregation in MSA, transgenic animal models and genetic strategies have been developed. Transgenic animal models allow the expression of alpha-synuclein in oligodendrocytes under control of specific promoters [Shults et al. 2005; Yazawa et al. 2005; Kahle et al. 2002]. The growing number of MSA animal models [Fernagut et al. 2005; Stefanova et al. 2005] opens up the possibility to create a basis for drug screening in human trials. The efficacy of neuroprotective drugs is assessed in rodent models before translation to clinical trials. Furthermore, transgenic models may be used to understand the alpha-synuclein aggregation process and allow screening for candidate drugs before further assessment in clinical trials [Waxman and Giasson, 2010; Ono et al. 2007]. Lithium is a first-line treatment for bipolar mood disorders [Beaulieu and Caron, 2008]. The set of evidence has grown to suggest that lithium may also have also some neuroprotective properties [Ferrucci et al. 2010; Beaulieu and Caron, 2008; Feng et al. 2008; Fornai et al. 2008].[36]

Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterized by the loss of motor neurons. Currently, no effective therapy is available to treat ALS, except for Riluzole, which has only limited clinical benefits. Stem-cell-based therapy has been intensively and extensively studied as a potential novel treatment strategy for ALS and has been shown to be effective, at least to some extent. In this article, we will review the current state of research on the use of stem cell therapy in the treatment of ALS and discuss the most promising stem cells for the treatment of ALS. The condition is the most common motor neuron disease, with a worldwide incidence of 2–3 per 100,000 and a prevalence at 4–6 per 100,000[37], posing a heavy burden on both the families involved and society at large. Patients tend to die 3–5 years after diagnosis due to progressive motor neuron loss and weakness of skeletal muscles, especially those muscles responsible for breathing, which is the primary cause of death caused by ALS. The pathogenesis of ALS is believed to be multifactorial. For the familial forms, several genetic mutations have been identified as being associated with the disease, including mutations in Cu superoxide dismutase (SOD1), TAR DNA binding protein-43 (TDP-43), the C9orf72

gene (the most common mutation underlying familial forms of ALS), and the recently discovered TBK1 gene encoding a protein involved in two essential cellular pathways of emerging interest in ALS research: autophagy and inflammation. [38]

NSCs originate from the neuroectoderm of early embryos and are found in embryonic, fetal, and adult nervous systems. They possess the potential to differentiate into any cell type in the central nervous system (CNS) (although NSCs derived from adult tissues show a more limited differentiation capacity. The integration ability and prospective therapeutic efficacy of human neural stem cells (hNSC) has been demonstrated in rodent models of neurological diseases. Apart from regenerating lost neuronal cells, NSCs can also improve the functional outcomes of rats through auxiliary mechanisms, such as neurotrophism and immunosuppression. Transplanted NSCs could differentiate into neurons and form synaptic connections with host tissues, delay disease onset and progression, and prolong the survival of experimental animals[39] Hefferan et al. found that grafted hNSCs protected adjacent motor neurons and helped to achieve transient functional improvement, and they speculated that this transient functional improvement was attained possibly because transplanted NSCs elicited neurogenesis and triggered intrinsic repair mechanisms in the spinal cord. More encouragingly, Teng and co-workers found that besides a delay in disease progression and an improvement in motor function, a quarter of the NSC-grafted ALS mice survived three times longer than their non-grafted counterparts. Given the pre-clinical support for NSC-based therapies, in 2009, the FDA approved a clinical trial on the safety and tolerability of surgical delivery of stem cells and any resulting cell toxicity. A total of 18 patients with ALS received an intraspinal fetal-derived NSC (NSI-566RSC) engraftment following a risk escalation paradigm, progressing from non-ambulatory to ambulatory subjects, lumbar to cervical spinal cord segments, and unilateral to bilateral injections across five cohorts. After monitoring the patients for 2.5 years, all patients tolerated the procedure without major surgical complications, such as injection-attributable neurological worsening, and there were no indications that the stem cells themselves were either toxic or injurious to the spinal cord. In an expansion of the above study using NSCs isolated from human fetal spinal cord tissues, Mazzini et al. transplanted human fetal brain tissues into the anterior horns of the spinal cord and additionally used a much higher cell dosage and a milder immunosuppression regimen. These studies have paved the way for future clinical trials on the efficacy and dosage of NSC treatment for ALS. A phase I clinical trial that began in July 2011 is designed to verify the safety of expanded hNSCs and microsurgery and to evaluate their effect on the quality of life of the patients. [40]

MSCs are multipotent adult stem cells that can be easily extracted from various adult connective tissues (i.e., bone marrow and adipose tissue) and can differentiate into a variety of cells. A number of studies

employing animal models of ALS have investigated the therapeutic potential of MSCs by injecting cells either peripherally or directly into the spinal cord. Assessed the efficacy of the systemic administration of adipose-derived mesenchymal stem cells (ASC) in SOD1-mutant mice and found that the cells not only significantly delayed motor deterioration for 4–6 weeks and maintained the number of motor neurons but also up-regulated the levels of glialderived neurotrophic factor (GDNF) and basic fibroblast growth factor (bFGF) in the spinal cord.

IPSCs can be derived from patients' somatic cells by reprogramming with specific factors. iPSCs express stem cell markers and have the ability to give rise to all three germ layers, as these cells are derived from adult somatic tissues they bypass ethical concerns, and so are promising candidates for stem cell therapy for ALS. [41]

Systemic Sclerosis

Systemic sclerosis (SSc) is a rare autoimmune disease, which is potentially lethal. SSc is a rare autoimmune disease, which affects most frequently middle age patients with a prevalence ranging from 100 to 300 per million depending on the country. The pathophysiology of SSc is still not completely understood even though three main axes of dysfunction are reported: fibrosis, vascular activation and immune abnormalities. The disease is characterized by vascular damage and diffuse fibrosis, which mainly affects skin and lung tissues but heart and digestive tract could also be involved. SSc is typically classified as limited or diffuse according to the extent and distribution of skin fibrosis. [42] One of the earliest and most frequent symptoms is the Raynaud's phenomenon but vasculopathy is also responsible of other clinical signs including digital ulcers, pulmonary arterial hypertension, and telangiectasia. All of these symptoms are responsible for increased morbidity and lead to functional disability (reduced mouth opening and loss of hand function, for example), pain, and psychological consequences. This impacts not only the patient's quality of life but also reduces his life expectancy. In at least half of the cases, patients will die from SSc-related disorders and the other half from higher incidence of malignancies and cardiovascular diseases compared to the general population.[43]

Mobilisation and collection of PBSC was achieved with cyclophosphamide (4 g/m2) in combination with granulocyte-colony stimulating factor (G-CSF), or G-CSF alone according to local protocol or when cardiac function with decreased LVEF prevented the use of cyclophosphamide.[44]

CONCLUSION

Many studies have now established the beneficial effect of the administration of BM-MSCs, ASCs or MSCs from other tissue sources in different preclinical models characterized by local or systemic fibrosis. Some evidence of safety and efficacy of MSC containing SVF or culture expanded MSCs has been described from the clinics but efficacy needs to be further proved in phase II clinical trials that are ongoing.

Both autologous and allogeneic MSCs from BM or adipose tissue are being assessed but the risk that the functional properties of MSCs isolated from SSc patients are altered is under debate. Contradictory results are reported in the literature but a number of reports discuss the reduction of the number of clonogenic cells, proliferative rate, differentiation, and angiogenic potentials. MSCs from SSc patients display a more mature and myofibroblast-like phenotype, probably related to micro environmental signals dysregulated during the disease. They express higher levels of TβRII and TGFβ, which is released into the extracellular medium where it can act in an autocrine or paracrine manner. Moreover, the crosstalk between MSCs and ECs contribute to the altered expression of different molecules involved in angiogenesis, inducing a switch of perivascular MSCs toward a myofibroblast population, further supporting the fibrotic process. The finding that MSCs from SSc patients constitutively overexpress mediators involved in the fibrotic and angiogenic processes might indicate that MSCs are altered by the environment secondary to the onset of the disease or, that they might participate to the physiopathology of the disease. With respect to the use of autologous MSCs for clinical applications, further investigation on their functional properties is likely needed.

CONFLICT OF INTEREST STATEMENT

We declare that we have no conflict of interest.

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REFERENCES

1. Davidson A, Diamond B. Autoimmune diseases. The New England Journal of Medicine. 2001; 345(5):340-350
2. Sampath B, Kathirvelu P and Sankaranarayanan K. Stem cell therapy and regenerative medicine in Autoimmune diseases. Intechopen. 2021; 10.5772/intechopen.89749
3. Mbobda DMJ, Yuan J, Wang J, Yan Y, Qian H, Zhang X, Mao F. MSC: Immunoregulatory effects, roles on neutrophils and evolving clinical potentials. Am J Transl Res. 2019; 11(6): 3890–3904.
4. Ferrara JL, Levine JE, Reddy P, and Holler E, "Graft- versus-host disease," The Lancet. 2009; 373(9674): 1550–1561.
5. Amorin B, Alegretti PA., Valim V, Pezzi A, Wieck A, Laureano M.A. Mesenchymal stem cell therapy and acute graft-versus-host disease. National library of medicine. 2014; 27(4):137-150.
6. Lin Y, Hogan WJ. Clinical application of mesenchymal stem cells in the treatment and prevention of graft-versus-host disease. National center for biotechnolology information. 2011; 10(12):1155-1160.
7. Lamb CA, Kennedy NA, Raine T, Hendy PA., Smith JP et al. British society of gastroenterology consensus guidelines on the management of inflammatory bowel

diseases in adults. Epub. 2019; 68(3):101-106.
8. Leighton JA, Shen B, Baron TH. ASGE guideline: endoscopy in the diagnosis and treatment of inflammatory bowel disease. Gastrointest Endosc. 2006; 6(3):558-65
9. Kim B, Barnett JL, Kleer CG et al. Endoscopic and histological patchiness in treated ulcerative colitis. Am J Gastroenterol. 1999; 9(4):3258-62.
10. Feakins RM. Inflammatory bowel disease biopsies: updated British society of gastroenterology reporting guidelines. J Clin Pathol. 2013; 6(6):1005-26.
11. Thurgate LE, Lemberg DA, Leach ST. An overview of inflammatory bowel disease unclassified in children. Inflammatory Intest Diseases. 2019;4(1):97-103
12. Feagan BG, Macdonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2012; 10:CD000543.
13. Ford AC, Kane SV, Khan KJ, et al Efficacy of 5-aminosalicylic in Crohn's disease: systematic review and metaanalysis. Am J Gastroenterol. 2011; 10(6):617-29.
14. Ford AC, Achkar JP, Khan KJ. Efficacy of 5-aminosalicylates in ulcerative colitis: systematic review and meta analysis. Am J Gastroenterol. 2011; 1(6):601-616.
15. Lennard JE, Longmore AJ, Newell AC. An assessment of prednisone, salazopyrin, and topical hydrocortisone hemisuccinate used as out-patient treatment for ulcerative colitis. Gut 1960; 1(3):217-222.
16. Truelove SC, Watkinson G, Draper G. Comparision of corticosteroid and sulphasalazine therapy in ulcerative colitis. Br Med J. 1962; 2(5321):1708-11.
17. Lennard-Jones JE. Classification of inflammatory bowel disease. Scand J Gastroenterol suppl. 1989;170:2-6.
18. Romberg-Camps MJ, Dagnelie PC, Kester AD. Influence of phenotype at diagnosis and of other potential prognostic factors on the course of inflammatory bowel disease. Am J Gastroenterol 2009; 104:371-83.
19. Moum B, Ekbom A, Vatn MH. Inflammatory bowel disease: re-evaluation of the diagnosis in a prospective population based study in south eastern Norway. Gut 1997; 40(3):328-32.
20. Freeman HJ. Use of the crohn's disease activity index in clinical trials of biological agents. World J of gastroenterol. 2008; 14(26):4127-4130.
21. Dziechciarz P, Horvath A, Shamir R et al. Meta-analysis: enteral nutrition in active Crohn's disease in children. Aliment Pharmacol Ther. 2007;26(6):795-806.
22. Khan KJ, Ullman TA, Ford AC, et al. Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis. AM J Gastroenterol. 2011; 106(4):661-73.
23. Chande N, Patton PH, Tsoulis DJ et al. Azathioprine or 6-mercaptopurine for maintenance of remission in chron's disease. Cochrane Database syst Rev. 2015; 10:CD000067.
24. Schoepfer AM, Bortolotti M, Pittet V et al. The gap between scientific evidence and clinical practice: 5-aminosalicylates are frequently used for the treatment of Crohn's disease. Aliment Pharmacol Ther. 2014; 40(8):930-7.
25. Akobeng AK, Zhang D, Gordon M et al. oral 5-aminosalicylic acid for maintenance

of medically-induced remission in Crohn's disease. Cochrane Database Syst Rev. 2016; 9:CD003715.
26. Malchow H, Ewe K, Brandes JW et al. European Cooperative Crohn's Disease Study (ECCDS): results of drug treatment. Gastroenterology. 1984;86(2):249-66.
27. Snowden JA, Panes J, Alexander T et al. Autologous haematopoietic stem cell transplantation in severe Crohn's disease: a review on behalf of ECCO and EBMT. J Crohns Colitis. 2018; 12(4):476-488.
28. Jiang Y, Jahagirdar BN, Reinhardt RL et al. Pluriopotency of mesenchymal stem cells derived from adult marrow. Nature 2002; 418(6893):41-9.
29. Satake K, Lou J, Lenke LG. Migration of mesenchymal stem cells through cerebrospinal fluid into injured spinal cord tissue. Spine 2004; 29(18):1971-9.
30. Fujiwara H et al. alpha-synuclein is phosphorylated in synucleinopathy lesions. Nat. Cell Biol. 2002;4(2):160-164.
31. Jellinger KA & Lantos PL. Papp-lantos inclusions and the pathogenesis of multiple system atrophy: an update. Acta Neuropathol. 2010; 119(6):657-67.
32. Scholz SW et al. SNCA variants are associated with increased risk for multiple system atrophy. Ann. Neurol. 2009; 65(5):610-14.
33. Tu PH et al. Glial cytoplasmic inclusions in white matter oligodendrocytes of multiple system atrophy brains contains insoluble alpha-synuclein. Ann Neurol. 1998; 44(3):415-22.
34. Kim C, Lee HJ, Masliah E & Lee SJ. Non-cell autonomous neurotoxicity of alpha-synuclein through microglial toll like receptor 2. Exp. Neurobiol. 2016; 25(3):113-119.
35. Flabeau O, Meissner W.G, Tison F. Multiple system atrophy: current and future approaches to management. Ther Adv Neurol Disord. 2010; 3(4):249-63.
36. Kuzdas-Wood D, Stefanova N, Jellinger KA, Seppi K. Towards translational therapies for multiple system atrophy. Prog Neurobiol. 2014; 11(8):19–35.
37. Chio A, Mora G, Calvo A, Mazzini L, Bottacchi E, Mutani R. Epidemiology of ALS in Italy: a 10-year prospective population based study. Neurology. 2009; 72(8):725-31.
38. Cirulli ET, Lasseigne BN, Petrovski S, Sapp PC, Dion PA, Leblond CS et al. Exome sequencing in amyotrophic lateral sclerosis identifies risk genes and pathways. Science. 2015; 347(6229):1436-41.
39. Xu L, Yan J, Chen D, Welsh AM, Hazel T, Johe K et al. Human neutral stem cell grafts ameliorate motor neuron disease in SOD-1 transgenic rats. Transplantation. 2006; 82(7);865-75.
40. Mazzini L, Gelati M, Profico DC, Sgaravizzi G, Projetti Pensi M, Muzi G et al. Human neural stem cell transplantation in ALS: initial results from a phase I trial. J Transl Med. 2015; 13(1):014-037.
41. Lei Ye, Cory Swingen, Jianyi Zhang. Induced Pluripotent Stem Cells and Their Potential for Basic and Clinical Sciences. Curr Cardiol Rev. 2013; 9(1):63-72.
42. LeRoy EC, Medsger TA Jr. Criteria for the classification of early systemic sclerosis. J Rheumatol. 2001; 28(7):1573-6.
43. Elhai M, Meune C, Boubaya M, Avouac J, Hachulla E, Balbir-Gurman A, et al. Mapping and predicting mortality from

systemic sclerosis. Ann Rheum Dis. 2017; 76(11):1897-1905.

44. Farge D, Passweg J, Van Laar JM et al. Autologous stem cell transplantation in the treatment of systemic sclerosis: report from the EBMT/EULAR registry. BMJ Journals. 2004; 63(8):974-981.