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REVIEW ARTICLE

Advances and prospects of cell therapy for spinal cord injury patients

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ABSTRACT

Spinal cord injury (SCI) is catastrophic damage for patients, their family, and society. Researchers and clinicians have been trying to find neurorestorative methods to recover their injured functions and structures. Cell therapy is one of the effective therapeutic strategies for SCI. And it can partially restore their neurological functions, which are once thought as permanent neurological deficits. Currently, cells being used therapeutically in clinic include olfactory ensheathing cells (OECs), mononuclear cells (MNCs), mesenchymal stromal cells (MSCs), Schwann cells, and hematopoietic stem cells, cell products differentiated from embryonic stem cells, mesenchymal stem cells, induced pluripotent stem cells, and neural stem cells as well as other kinds of cells. Real world data from these cell therapies showed some benefits in some patients with SCI. Due to being affected by many factors, the therapeutic results of some kinds of cells are contradictory and it is hard to compare effects among different types of cells. According to the data of cell therapies, OEC, MNC and MSC transplantation are applied for patients in majority percentage of cases, and OEC transplantation had a higher percentage of benefits. In next step, under the unified standard of cell preparation and quality control as well as the guidelines of clinical cell application, each kind of cells including OECs should be studied using prospective, multicenter, double-blind or observing-blind, placebo-control, randomized studies for SCI patients with different level of injury and chronicity.

1 Introduction

To restore the damaged neurological functions and structures after spinal cord injury (SCI) is still a challenging work. Previous thought permanent neurological deficits following SCI

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have been partially restored by cell therapy, neuromodulation and brain–machine interface, nerve grafting or reconstruction and other neurorestorative therapeutic strategies in clinical studies [1]. Cellular therapies are the effective treatments for patients with SCI. In this review we briefly introduce their developmental process and recent progresses in this field.

2 Cell types for clinical cell therapy

According to cell categories by the United States Food and Drug Administration (US FDA; Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products, November 2013; https://www.fda.gov/media/87564/download), cell therapies are divided into mature/functionally differentiated cell-derived cell therapy products and stem cell-derived cell therapy products. Clinical studies have tested many cell therapies for patients with SCI, which include functional or mature cells, such as olfactory ensheathing cells (OECs), mononuclear cells (MNCs), mesenchymal stromal cells (MSCs), Schwann cells (SCs) as well as others; and stem cells products, such as hematopoietic stem cells (HSCs), cell products differentiated from embryonic stem cells (ESCs), mesenchymal stem cells, induced pluripotent stem cells (iPSCs) and neural stem cells (NSCs).

2.1 Olfactory ensheathing cells

Olfactory ensheathing cells are novel cells, which have the functions of SCs and astrocytes [2]. Huang et al. first reported in 2002 that transplanting OEC from aborted fetal olfactory bulbs into the spinal cord parenchyma in adjacent to the injured site in 23 patients with chronic SCI (19 complete and 4 incomplete) [3]. It demonstrated improvements of patients' neurological functions and the quality of life during 2-week and 2-month follow-up in a prospective pilot study. Most patients showed a trend towards improvement after cell therapy. Following this study, a series of retrospective reports proved the safety and neurorestorative effects of OEC transplantation [4–10]. One of retrospective reports showed neurological functional improvements in 537 of 566 (94.88%) patients with chronic SCI [8]. In another long-term follow-up retrospective study, patients with chronic complete SCI showed better recovery of neurological functions and improvements of the quality of life in patients gained sufficient neurorehabilitation compared with those gained insufficient neurorehabilitation [9]. OECs combination with Schwann cells showed better functional restoration than single kind of cell therapies for patients with chronic complete SCI in a prospective randomized double-blind trial [10]. Rabinovich et al. in 2003 reported that OECs and hemopoietic cells were subarachnoidally implanted into 15 patients (18–52 years old) with complete SCI after 1 month to 6 years in a retrospective study [11]. Patients underwent one to four times of cell transplantation; 11 of 15 cases showed motor and sensory improvements. Long-term following-up found that 48.9% cases improved independence. The best results were observed within the first 2 years after cell therapy and in younger individuals [12]. Mackay-Sim's team (2005 and 2008) reported that transplanting about 0.5 mL liquid containing autologous OECs into spinal cord parenchyma did not show functional improvement in 2 out of 3 patients with paraplegia in a prospective open label study [13, 14]. It was possibly because of the damage from the procedure itself (too many injections with big liquid volume) [15]. Sun's team (2006) reported that injecting OECs into spinal cord parenchyma showed functional improvement in 11 patients with chronic complete SCI in over 1-year following-up in a retrospective study [16]. Zheng et al. (2007) reported that 106 patients

with different chronicity, types and sites of injury showed varying benefits after injecting OECs into the spinal cord parenchyma in adjacent to the injury in a retrospective study; assessment by Frankel Grade showed improvement in 45 of 106 patients [17]. Subsequently published papers corroborated with the results [18, 19]; especially the one with 7-year follow-up, majority patients showed improvements of neurological functions and the quality of life [19]. Bao et al. (2007) reported that 5 patients with complete SCI after 3 months to 1 year received OEC transplantation in a retrospective study; 4 of 5 patients remarkably improved motor and sensory functions [20]. Rao et al. (2013) reported 8 patients with cervical SCI got OEC therapy in a retrospective study and majority improved motor function, sensation and urine control function [21]; 6 patients showed neurological improvement in 2-year follow-up [22]. In another study, 15 patients with sub-acute SCI improved neurological functions after OEC treatment [23]. Tabakow et al. (2013) reported that transplantation of autologous OECs and olfactory nerve fibroblasts in 3 patients with chronic complete thoracic SCI showed neurological improvements in a phase I clinical trial [24]. A 38-year-old man sustained traumatic transection of the thoracic spinal cord got transplantation of autologous OECs and olfactory nerve fibroblasts; the injury gap was bridged by four strips of autologous sural nerve. His trunk stability, voluntary movements of the lower extremities, and sensation improved after 19 months of treatment [25]. He's team (2021) reported that 8 of 13 patients showed neurological improvements after 10-year follow-up in a retrospective study [26]. However, Zamani et al. (2021) reported no improvement in sensory scores in 2 of 3 patients with chronic complete SCI and no motor in all 3 participants after OEC and bone marrow MSC co-transplantation through the lumbar puncture in a phase I clinical trial [27]. Lima et al. (2006) reported that transplanting olfactory mucosa autograft into injured area showed neurological improvements in 15 of 20 patients with chronic SCI in a prospective, uncontrolled pilot study [28, 29]. Repeating Lima's technique in India on 5 patients did not get same results [30]; but in Japan, 5 of 8 patients with chronic complete SCI improved their neurological functions [31]. In the sham control study, even 2 of 8 patients with chronic complete SCI showed some improvements of motor and sensation; but there were no remarkable differences in assessing neurological functions between treated and control groups [32]. A mass formation was found following olfactory mucosal tissue transplantation. The mass kept increasing and therefore pressed or impaired surrounding nerves, and it caused neurological symptoms [33, 34].

At present, there are many clinical studies on OECs, but more high-level evidence is needed for further confirmation. In addition, the reliable source of clinical cells also needs to be strengthened.

2.2 Mononuclear cells

The advantage of autologous bone marrow MNCs is easy to obtain. Park et al. (2005) reported that in conjunction with the administration of granulocyte macrophage-colony stimulating factor, autologous bone marrow MNCs were injected into injured sites in 5 patients with acute complete SCI in a pilot study; most patients showed neurological improvements [35]. Syková et al. (2006) reported that autologous bone marrow MNCs were infused via spinal arteries close to injured cervical spinal cord or intravenous administration in 20 patients with complete SCI from 10 to 467 days in a pilot study; the cell transplantation as well as the procedure was safe [36]. Yoon et al. (2006) reported that the bone

marrow MNCs were transplanted by injection into the surrounding area of the SCI sites in 35 patients with complete SCI in a phase I/II clinical trial, 7 of 23 patients in acute and sub-acute stage, and no patients in chronic stage improved their neurological functions [37]. Chernykh et al. (2007) reported that transplantation of bone marrow MNCs showed improvement of sensory and motor activity and conducting sensory function in patients with chronic SCI in a prospective open label control trial [38]. Cristante et al. (2008) reported autologous undifferentiated peripheral blood MNCs were infused through arteriography in 39 patients with chronic SCI in a prospective, non-randomized clinical trial; 26 of 39 showed recovery of the somatosensory evoked response to peripheral stimuli after 2.5 years of follow-up [39]. Kumar et al. (2009) reported that autologous bone marrow MNC therapy in 297 patients with SCI through a lumbar puncture in a retrospective study; 97 of 297 patients showed sensory and motor improvements [40].

In recent 10 years, there have been many research reports of MNCs used in treating SCI. El-Kheir et al. (2014) reported that 50 chronic cervical and thoracic SCI patients, the injury durations of whom were at least 12 months, were treated with intrathecal injection of autologous bone marrow MNCs combined with physical therapy in a phase I/II controlled single-blind clinical trial; 23 of 50 cases showed sustained functional improvement [41]. Sharma et al. (2014) reported that a patient had functional recovery in chronic stage of SCI following autologous bone marrow MNC therapy [42]. Sharma et al. (2013) reported a retrospective study that 56 patients with chronic cervical SCI treated got intrathecal transplantation of MNCs along with neurorehabilitation in the following 2 years or more [43]. The study showed that 92% of the patients improved after treatment; their symptoms such as trunk stability, sitting balance, trunk muscle strength, upper limb strength, standing balance, deep touch sensation, bladder sensation, spasticity and walking balance demonstrated improvements. There was statistically significant difference in the Functional Independence Measure (FIM) scale post intervention and no serious adverse events were reported. Another report published by Sharma et al. in 2013 describes the results of intrathecal MNC transplantation for thoracolumbar SCI in a retrospective study [44]. 110 patients were treated out of which 91% improved. There was a statistically significant improvement in FIM scores, reduction in spasticity, partial sensory recovery, and improvement in trunk control, postural hypotension, bladder management, mobility, activities of daily living, and functional independence. Some patients showed a shift on the American Spinal Injury Association (ASIA) scale and changes in electro-physiological studies or functional magnetic resonance imaging (MRI). No major side effects were noted. In 2020, they reported that 180 patients with sub-acute and chronic SCI showed symptomatic improvement in sitting/standing balance, bed mobility, trunk stability, upper limb function, mobility, sensation, bowel/bladder functions, and activities of daily living after administering bone marrow MNC through lumbar puncture in a retrospective study. Younger patients or patients applied with additional bone marrow MNCs (more than one dose) in early intervention demonstrate better functional outcome; 125 of 180 patients improved their quality of life [45]. Zhu et al. (2016) reported that umbilical cord blood MNC transplant therapy combining locomotor training in patients with chronic complete SCI improved scores of walking index of SCI and Spinal Cord Independence Measure (SCIM) in a phase I/II clinical trial; 15 of 28 patients improved their quality of life [46]. Kakabadze et al. (2016) reported in a clinical trial of autologous bone marrow MNC transplantation

of patients with complete motor deficit SCI in a phase I clinical trial; 9 of 18 cases showed better neurological improvement than others [47]. Liem et al. (2018) reported that transplantation of bone marrow MNC for 2 patients with SCI from spina bifida could improve bowel function [48]. Srivastava et al. (2019) reported that 70 patients with acute SCI after bone marrow MNC infusion into subarachnoid space got significant motor neurological recovery compared to the control patients in a randomized controlled trial [49].

Xiao et al. (2016) reported that following scar resection, implanting scaffold with autologous bone marrow MNCs in 5 patients with complete chronic SCI showed partially autonomic nervous function improvement in 1-year follow-up in a pilot study [50]. In another pilot study, same method was applied in 7 patients with acute complete SCI, partial shallow sensory and autonomic nervous functional improvements were observed in some patients, but no motor function recovery [51]. There are many published studies on clinical research of this cell type, but there is also a lack of high-level evidence.

Derakhshanrad et al. (2018) reported their phase II/III, prospective, double-blind, placebo-controlled, parallel randomized clinical trial [52]. They performed 7 daily subcutaneous granulocyte colony-stimulating factor (G-CSF) administration for 60 patients with incomplete subacute traumatic spinal cord injuries, in which the mechanism was the mobilizing MNCs. With assessment before intervention and at 1, 3, and 6 months, patients showed significant motor, sensory, and functional improvement after administration of G-CSF. Derakhshanrad et al. (2018) also reported a phase III, double-blind, randomized controlled clinical study of administration of G-CSF for 120 patients with incomplete chronic SCI. A significant difference was observed in motor, sensory, and functional improvement between G-CSF group and placebo group [53].

2.3 Mesenchymal stromal cells

Mesenchymal stromal cells have more clinical research reported in the SCI treatment than other type of cells. Its advantages are abundant sources, easy culture and preparation procedure. The quality control is gradually improved and consensus has been reached. According to the criteria set up by the International Society for Cellular Therapy, the MSC criteria are: (1) MSC must be plastic-adherent when maintained in standard culture conditions; (2) MSC must express CD105, CD73, and CD90, and lack expression of CD45, CD34, CD14 or CD11b, CD79alpha or CD19 and HLA-DR surface molecules; and (3) MSC must differentiate to osteoblasts, adipocytes and chondroblasts *in vitro* [54, 55]. In this review, we use MSCs to refer mesenchymal stem cells which were identified by authors using the MSC criteria.

Kang et al. (2005) reported that umbilical cord MSC transplantation for a female patient with SCI showed improvement of sensory perception and mobility [56]. Geffner et al. (2008) reported that administration of autologous bone marrow MSCs for 8 patients with SCI via multiple routes was safe, and it improved their quality of life in retrospective study [57]. Pal et al. (2009) reported that transplantation of *ex vivo*-expanded autologous bone marrow-derived MSCs in 23 patients with SCI was safe with no serious adverse events in over 1-year following-up in a pilot study; but they did not assess neurological functions [58]. Kishk et al. (2010) reported that intrathecal autologous bone marrow MSC could improve some neurological functions in 44 patients with chronic SCI in a control study; but improvements showed no significant difference compared with the control group [59]. Park et al. (2012) reported that directly injecting autologous bone marrow MSCs into both spinal cord and the intradural space in 10 patients with SCI in a pilot study; 6 of 10 showed improvements in the motor power

of the upper extremities and in activities of daily living, as well as significant MRI and electrophysiological changes during long-term follow-up [60]. But in their phase III study (2016), most patients did not improve damaged neurological functions [61]. Liu et al. (2013) reported intrathecal injection of umbilical cord MSCs in 22 patients with incomplete SCI in a pilot study, 13 of 22 cases improved neurological function and quality of life [62]. Dai et al. (2013) reported that 19 of 20 patients with chronic complete cervical SCI after bone marrow MSC transplantation improved their neurological function and quality of life in a prospective control study [63]. Oraee-Yazdani et al. (2013) reported that transplantation of autologous MSC and SC combination directly into the injury site had negligible sensory (no motor) improvement in 3 of 8 patients with chronic complete SCI in a pilot study [64]. In their following studies, combining cell transplantation through lumbar puncture, 1 of 6 patients with chronic complete SCI had sensory improvement (2016) [65]; 8 of 11 patients with sub-acute complete SCI had sensory and motor improvements (2021) [66]. Mendonça et al. (2014) reported that 14 patients with chronic complete SCI after intralesional transplantation of autologous transplantation of bone marrow MSCs improved sensation in a pilot study, 8 of 14 cases improved motor functions [67]. Chotivichit et al. (2015) transplanted autologous bone MSCs tracked by MRI in a patient with chronic SCI. Patients did not show functional improvement, even tagged cells were found at the surface around his cervical spinal cord [68]. Satti et al. (2016) reported that intrathecal injection of autologous MSC transplantation in 6 patients with complete SCI was safe [69]. Vaquero et al. (2016) reported autologous bone marrow MSC transplantation in 12 patients with chronic complete paraplegia in a pilot study; all patients experienced improvement including sensitivity, sphincter control, motor activity, decreases in spasms and spasticity, improved sexual function [70]. They (2017 & 2018) found that repeated subarachnoid administrations of autologous MSCs in patients with incomplete SCI were able to achieve progressive improvement and significantly improved the quality of life [71, 72]. Also, this kind of cell therapy could relieve neuropathic pain due to SCI (2018) [73], reduce syrinx and show clinical improvements for post-traumatic syringomyelia (2018) [74]. Larocca et al. (2017) reported that image-guided percutaneous intralesional administration of MSCs in 5 patients with chronic complete SCI showed some functional improvement in a pilot study [75]. Guadalajara et al. (2018) reported that autologous MSC transplantation into the subarachnoid space in a patient with SCI demonstrated the improvement of neurogenic bowel dysfunction [76]. Santamaría et al. (2019) reported that intrathecal injections of bone marrow stromal cells in a patient with C2 tetraplegia showed clinical and neurophysiological improvement [77]. Direct parenchymal injection to the affected lesion and multiple (5 times) intravenous injection in a patient with a 12-year-long-chronic SCI showed his neurological status improvement [78]. A patient with incomplete chronic SCI through intrathecal administration of adipose tissue-derived MSCs showed meaningful neurological improvement [79]. Repeated subarachnoid administrations of umbilical cord MSCs in 41 patients with SCI lead to significant improvement in assessing neurological dysfunction and the quality of life in a phase 1/2 pilot study [80]. Intrathecal transplantation of umbilical cord MSCs in 5 patients with chronic complete SCI induced sensory improvement in the segments adjacent to the injury site in a randomized controlled study, but no motor improvement [81].

Bryukhovetskiy reported in 2015 that implanting biodegradable polymer SpheroGel with

autologous cells in 50 patients with chronic complete anatomic defect SCI; 25 of 50 patients improved motor functions of limbs [82]. Zhao et al. (2017) implanted scaffold with umbilical cord MSCs following scar resection in 8 patients with chronic complete SCI in a prospective uncontrolled study, some functional improvements were observed in some patients during 1 year of follow-up [83]. The same procedure was applied in 2 patients with acute complete SCI, who showed partial recovery of the sensory and motor functions (2018) [84]. A retrospective study reported that a 2- to 5-year follow-up observation showed some functional improvements in one third patients with acute complete SCI and also in nearly half of the patients with chronic complete SCI in [85].

2.4 Schwann cells

Saberi et al. (2008) reported that autologous SC transplantation for 4 patients with chronic thoracic SCI was safe in a pilot study, but beneficial effects was not shown [86]. Long-term observations found that intramedullary cell transplantation was safe in 33 patients with chronic SCI, but effects was not assessed in a prospective uncontrolled study [87]. Zhou et al. (2012) reported that transplantation of autologous activated SCs in 6 patients with chronic SCI improved some functions with 5 years of follow-up in a retrospective study [88]. Autologous purified Schwann cell transplantation into the injury epicenter of 6 participants with subacute complete thoracic SCI showed no clinical improvements in an open-label, unblinded, non-randomized, non-placebo controlled study [89]. However, a following study found thoracoabdominal motor connectivity in all 6 patients, which was detected by longitudinal electrophysiological assessment [90]. In another phase I safety trial, Gant et al. (2022) implanted SCs in 8 patients with chronic SCI (4 complete and 4 incomplete), one of them demonstrated partial motor and sensory function improvement [91].

2.5 Hematopoietic stem cells

Hematopoietic stem cells are also proved to be beneficial to SCI by basic research. Deda et al. (2008) reported a direct injection of autologous bone marrow HSCs in 9 patients with chronic SCI showed improvements of movements and sensations in apilot study [92]. Al-Zoubi et al. (2014) transplanted purified autologous leukapheresis-derived CD34+ and CD133+ stem cells in 19 patients with chronic complete SCI in a retrospective study; nearly half patients demonstrated segmental sensory or motor improvement during long-term evaluation follow-up [93]. Ammar et al. (2017) reported using biological scaffold with autologous HSCs and platelet-rich protein for 4 patients with SCI in a pilot study, one of them showed motor and objective sensory improvement during a period between 2- and 3-year follow-up [94].

2.6 Cells differentiated from embryonic stem cells

In vitro differentiation of embryonic stem cells is a direction of cell drug research. Scott and Magnus (2014) described that the first clinical trial from the Geron Company about oligodendrocytes differentiated from human embryonic stem cells started and stopped. Enrolled patients did not get benefits from this trial [95].

2.7 Cells differentiated from mesenchymal stem cells

Some studies have also explored the transmesodermal differentiation of mesenchymal stem cells into ectoderm. Thakkar et al. (2016) reported that transplantation of autologous adipose tissue derived mesenchymal stem cell differentiated neuronal cells and bone marrow HSCs in 10 patients with chronic SCI in a retrospective study;

all 10 patients were noted variable and sustained improvement during follow-up [96].

2.8 Cells differentiated from neural stem cells

Transplantation of NSCs is a hot research topic. Shin et al. (2015) reported that transplanting neural stem/progenitor cells in19 patients with chronic SCI in a phase I/IIa open-label and nonrandomized controlled clinical trial, 5 of 19 cases showed modest neurological benefit [97]. Transplanting NSC (NSI-566) in 4 patients with chronic SCI showed one to two levels of motor and sensory improvements in 2 of 4 subjects (2018) [98]. Levi et al. (2018) reported that perilesional intramedullary injections of human central nervous system stem cell (HuCNS-SC) from fetal brain in thoracic and cervical SCI proved safe and feasible in a phase I trial [99]. Transplanting HuCNS-SCs by using this technique in 12 participants with cervical chronic SCI in an effective study, a few patients showed small motor gains; but at a magnitude below the required clinical efficacy threshold (2019) in a phase II single blind, randomized proof-of-concept study [100]. Transplanting HuCNS-SCs into injured thoracic cord in 12 patients with chronic SCI demonstrated safety. Six-year follow-up data showed reliable sensory improvements in 5/12 patients, unfortunately, without motor improvement (2020) in a phase I/IIa trial [101].

2.9 Cells differentiated from iPSCs

Although iPSCs make people full of expectations, currently there is no clinical report of cells differentiated from iPSCs for SCI. There is only a clinical study protocol which focuses on safety of human iPSC-derived neural stem/progenitor cell for SCI [102].

2.10 Other cells

There are other types of cells that have also been used in clinical studies of spinal cord injury. Moviglia et al. (2006) reported that combined protocol of cell therapy (autoimmune T cells and NSCs) transdifferentiated from bone marrow MSCs in 2 patients with chronic complete SCI showed motor and sensory improvements with an evaluation of the electrical and clinical functional assessment [103]. In another pilot study (2009), they treated 8 patients with chronic complete SCI (5 with jeopardized brachial plexus). The procedure as below: (1) apply selective artery infusion of bone marrow MNCs to the disrupted area for vascularization recovery; (2) inject through an i.v. infusion of spinal cord specific effector T cells for restoring the specific inflammatory activity; (3) infuse autologous NSCs through selective feeding artery for damaged neurological repair. Seven patients exhibited motor and sensory improvements [104]. Moviglia et al. (2018) reported that local transplantation of autologous type 1 macrophages, autologous tissue-specific T helper 1 cell and autologous muscular progenitor cells in 7 patients with atrophied muscles caused by SCI showed progressively increasing muscle volume and gradually replacement of hyperechogenic muscle tissue in a pilot study [105].

2.11 Reports of cell therapy with more than 10 patients

We have summarized reports of cell therapy with more than 10 patients in Table 1, in which cell type, research team or authors, cases and improved cases are listed.

3 Routes of clinical cell therapy

Different cell types are suitable for different cell transplantation routes. Many cell transplantation routes were tried, such as subcutaneous, intravenous, subarachnoid, intracerebral, intraspinal, intramuscular and submucosal. With the

Table 1 Summary of selected reports of cell therapy for SCI patients.

Cell type	Team [Ref]	Cases	Improving cases
OEC	Huang [8]	**566**	**537**
OEC & Hemopoietic cells	Rabinovich [12]	15	11
OEC	Sun [16]	11	11
OEC	Zheng [17]	**106**	**45 (Frankel Grade)**
OEC	Rao [23]	15	15
OEC	He [26]	13	8
Olfactory mucosa	Lima [29]	20	15
MNC	Syková [36]	20	Safe, no available data for effect
MNC	Yoon [37]	35	7
MNC	Cristante [39]	39	26
MNC	Kumar [40]	**297**	**97**
MNC	El-Kheir [41]	50	23
MNC	Sharma [45]	**180**	**125**
MNC	Zhu [46]	28	15
MNC	Kakabadze [47]	18	9
MNC	Srivastava [49]	70 (control 68)	55 (control 43)
MNC (Mobilized by G-CSF)	Derakhshanrad [52]	28 (control 26)	A significant improvement in G-CSF group
MNC (Mobilized by G-CSF)	Derakhshanrad [53]	56 (control 58)	A significant difference between the two groups
MSC	Pal [58]	23	Not available
MSC	Kishk [59]	44	No difference with control
MSC	Jeon [61]	16	2
MSC	Liu [62]	23	13
MSC	Dai [63]	20	19
MSC & SC	Oraee-Yazdani [66]	11	8
MSC	Mendonça [67]	14	8
MSC	Vaquero [70]	12	12
MSC	Yang [80]	41	No available data of patients got improved. Scores improvement in all assessments
SpheroGel with MSC	Bryukhovetskiy [82]	50	25
Scaffold with MSC	Tang [85]	66	35
SC	Saberi [87]	33	Safe, no available data for effect
CD34+ and CD133+ stem cell	Al-Zoubi [93]	19	9
Neuronal cell differentiated from MSC and bone marrow HSCs	Thakkar [96]	10	10
Cell differentiated from NSC	Shin [97]	19	5
HuCNS-SC	Levi [100]	12	Terminated early due to under the required clinical efficacy threshold
HuCNS-SC	Curt [101]	12	5

Note: The reports summarized in this table are cell therapy with more than 10 cases. One article which reports more cases is elected from each team except clearly judging data from different treated groups. Patients with OEC, MNC and MSC transplantation contributed more cases and OEC transplantation has a higher percentage of benefits among cell therapies.

development of science and technology, many safer methods were used. More clinical trials need to be performed to find the best routes for different cells in the future.

4 Assessment recommendation

American Spinal Injury Association (ASIA) Impairment Scale (AIS) is often applied to assess and evaluate the condition of neurological functional damage in patients with SCI. There are many assessments evaluating the quality of life or disability degree in patients with SCI, such as Functional Independence Measure (FIM), Spinal Cord Independence Measure (SCIM), Walking Index for Spinal Cord Injury (WISCI), Quadriplegia Index Function (QIF), Frankel Grading, Barthel Index, International Standards to document remaining Autonomic Function after Spinal Cord Injury (ISAFSCI), International Association of Neurorestoratology-Spinal Cord Injury Functional Rating Scale (IANR-SCIFRS) [9], etc.

Here we recommend AIS as an assessment tool for neurological functions of SCI, because it can accurately reflect the neurological situation of patients with SCI. We suggest IANR-SCIFRS as an assessment tool for the quality of life of SCI patients, because it is a simple, precise, comprehensive method to assess the quality of life for patients with SCI. This method can be easily mastered to use by patients themselves or their caregivers.

5 Key issues that need to be addressed

5.1 Cell name obfuscation

One kind of cells is often called different name in different articles by same authors or different authors, such as (1) MNCs are miscalled as stem cells; (2) MSCs are miscalled as mesenchymal stem cells, but using MSC criteria [54, 55] as the identification and quality control standard. We recommend authors to correctly use cell name in their future articles.

5.2 Contradictory results

As we well know, the neurorestorative effects of each kind of cells depend on many factors, such as neurorestorative ability of the cell itself, the cell status, indication of diseases or their time window, dosage, transplanting route, treating times and interval time. In this review, almost all kinds of cells except OECs demonstrated positive or negative results in patients with acute, sub-acute or chronic and complete and incomplete SCI. Same kind of cells might show different results in different articles by same team or different teams. Even OECs showed positive results in majority clinical studies for most patients with SCI, but still a few patients did not get benefits from the OEC transplantation. In following clinical cell studies, we suggest: (1) the cell preparation and transplanting procedure should follow or conform to the standards and guidelines which have been set up and applied for in clinic [106–108], especially paying attention on the cell status according to criteria for assessing the state of cells; (2) in order to firmly prove the neurorestorative effects or get better benefits, prospective, multicenter, double-blind or observing-blind, placebo-control, randomized clinical cell therapy trials should be performed, especially for cells which have shown positive results for patients with SCI in previous clinical studies.

5.3 Prohibiting resecting injured cord tissue

Tissue engineering materials with cell therapy are possible potential tools for neurorestoration in patients with SCI [50, 51, 82–85]. However, many patients with acute and sub-acute complete SCI can restore their neurological functions spontaneously or with neurorestorative therapies

[49]. Even more patients with complete chronic SCI have demonstrated partially restoring standing, walking abilities and other improvements of daily living activities through neurorestorative therapies with intensive neurorehabilitation [1, 9]. Total resecting injured spinal cord may possibly deprive neurorestorative chances in SCI patients; so International Association of Neurorestoratology (IANR) and Chinese Association of Neurorestoratology (CANR; Preparatory) suggest prohibiting resecting injured cord tissue for implanting materials [109, 110]. Implanting tissue engineering materials should be reserved for SCI patients with total anatomical defect [82].

5.4 Neurorestorative mechanisms of cell therapies

All kinds of cells have some common mechanisms of neurorestoration, such as more or less cellular paracrine effects and exosomes which affect or mediate the changes in the microenvironment of injured site. OEC is a very special kind of glia which shares characteristic of SC and astrocyte; it has strong paracrine ability and could secrete such as neurotrophic factors. Also it is well known for its' neurorestorative mechanisms, that is, neuroprotection, axonal regeneration, remyelination, neural network or circuitry reconstruction, neuroplasticity, neuromodulation, anti-inflammatory response or immunomodulation, promoting neurogenesis, stimulating angiogenesis, etc. [2, 6].

6 Conclusions and prospect

Cell therapies have been applied to treat SCI patients since 2001. Currently over ten kinds of cells have been tested effects for SCI. Real world data of most cell therapies showed some benefits for some patients with SCI. Due to being affected by many factors, such as neurorestorative ability of cell itself, indication of diseases or their time window, dosage, transplanting route, treating times and interval time, the therapeutic results of some kinds of cells are contradictory.

Additionally, it is hard to compare the effects of cell therapies among all kinds of cells, because of the influence of many affecting factors, such as injured segments (cervical, thoracic, lumbar), degree (complete or incomplete), period (acute, sub-acute or chronic) and assessment tools. Seen from the data in the Table 1, relative more patients got OEC, MNC and MSC transplantation, and OEC transplantation had a higher percentage of benefits among cell therapies.

In the next step, under the unified standard of cell preparation and quality control as well as the guidelines of clinical cell application, prospective, multicenter, double-blind or observing-blind, placebo-control, randomized clinical trials for each type of cells including OECs should be carried out in patients with SCI to evaluate efficacy. Factors like level and chronicity of injury should be further evaluated.

Conflict of interests

The authors report no conflict of interests in this work except Huang H holds the patent on OEC culture method in Beijing Hongtianji Neuroscience Academy.

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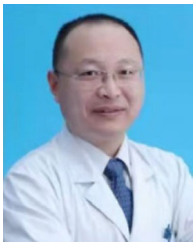

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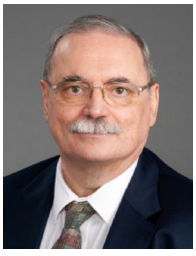

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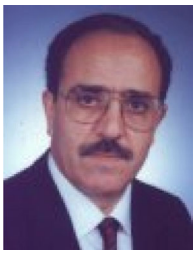

Ziad Al-Zoubi, honorary professor in Basrah University, Jordan; consultant of spinal and orthopaedic surgery; honorary president of IANR; honorary president of the Pan Arab Spinal Society. He focuses on neurorestoration for neurological, muscular and skeletal disorders through cell therapy and other novel techniques.

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