Cell therapies for spinal cord injury: trends and challenges of current clinical trials.

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ABSTRACT:

Cell therapies have the potential to revolutionise the treatment of spinal cord injury. Basic research has progressed significantly in recent years, with a plethora of cell types now reaching early-phase human clinical trials, offering new strategies to repair the spinal cord. However, despite initial enthusiasm for preclinical and early phase clinical trials, there has been a notable hiatus in the translation of cell therapies to routine clinical practice. Here, we review cell therapies that have reached clinical trials for spinal cord injury, providing a snapshot of all registered human trials and a summary of all published studies. Of registered trials, the majority have used autologous cells and approximately a third have been government funded, a third industry sponsored, and a third funded by university or healthcare systems. A total of 37 cell therapy trials have been published, primarily using stem cells, although a smaller number have used Schwann cells or olfactory ensheathing cells. Significant challenges remain for cell therapy trials in this area, including achieving stringent regulatory standards, ensuring appropriately powered efficacy trials, and establishing sustainable long-term funding. However, cell therapies hold great promise for human spinal cord repair and future trials must continue to capitalise on the exciting developments emerging from preclinical studies.

KEY WORDS:

MAIN ARTICLE:

Background

Cell therapies are a promising treatment for spinal cord injury (SCI). They may act through complementary mechanisms, including neuroprotection, trophic factor release, immunomodulation, axon regeneration and myelin regeneration to promote recovery of function after SCI.[1-3] A number of cell therapies have been trialled for spinal cord repair, yet there remain no approved treatments available for patients with SCI. This review discusses recent advances using cell therapies for human SCI and considers the challenges associated with translating exciting new scientific advances in this field to meaningful, practice-changing clinical therapies.

A snapshot of the current clinical trial landscape

A review of clinicaltrials.gov revealed that there are currently 49 registered clinical trials exploring the use of cell therapies for spinal cord repair (search strategy outlined in Supplementary Information). The first trials were registered in the early 2000's and the number of trials has continued to rise, but there has been a particularly striking increase since 2010 (Figure 1a). A variety of different cell types have been used, but mesenchymal stem cells (MSCs) and mononuclear progenitor cells (MNCs) have dominated registered clinical trials – an overview of all cell types is summarised in Table 1. A smaller number of more recent trials have also begun to explore neural stem cells (NSCs), along with Schwann cells (SCs), olfactory ensheathing cells (OECs) and oligodendrocyte precursor cells (OPCs). The rate at which MSC and MNC trials were registered after 2016 appears to be slowing (Figure 1b), possibly due to inherent variation in annual

numbers or because of a saturation in clinical research capacity worldwide. The majority of trials remain ongoing or uncompleted, although the greatest number of trials have been completed using MSCs (Figure 1c). Of all registered trials, the majority (63%) have used cells derived from autologous sources, whilst 27% have used allogenic cells (Figure 1d). Autologous cells mitigate the need for immunosuppression, but may be associated with donor site morbidity and inherent variability between patients. In contrast, allogeneic cells can be mass produced to a consistent standard, but may require immunosuppression to prevent immune rejection[4]. Concerningly, 10% of trials do not clearly state the source of cells used.

Cell therapy trials for SCI are currently taking place in 19 countries across the globe (Figure 2a), with approximately half of all trials registered in Asia (Figure 2b). India and China surpass all other countries in terms of the numbers of patients estimated to be enrolled, with 764 and 542 patients, respectively (Figure 2c). They also have the highest number of trials registered, with six trials in India and nine in China, followed by five in the USA. This likely reflects large population sizes and the significant unmet clinical need due to a high SCI burden in low and middle income countries.[5]

Despite there being a significant number of registered trials, the overwhelming majority remain at an early stage (Figure 3a). 96% of registered trials are either phase I, phase II or nested phase I/II designs, with the significant majority being single-site studies (84%). Consequently, most trials are aiming to recruit relatively few patients, although three trials expect to recruit more than 100 patients (Figure 2c). Current trials mainly focus on assessing the feasibility and safety of cell transplantation, although some report functional recovery as the primary outcome. In contrast to what might be expected for early-phase drug trials, only a small

number of trials have incorporated specific dose-ranging or toxicity studies. Most trials remain ongoing or not completed (Figure 3b).

Only a minority of trials (43%) have been registered prospectively, as defined by registration on clinicaltrials.gov prior to the study start date (Figure 3c). This leaves considerable scope for improvement, yet the prospective registration rate for SCI cell therapy trials is higher than the 31% average that has been previously noted for clinical trials more generally.[6] The number of completed trials linked to publications on clinicaltrials.gov is low at 28% (Figure 3d). This figure may be an underestimate due to the delay between trial completion and subsequent publication; however it is still considerably less than the 50-75% publication rate that has been reported for clinical trials in other areas, even when accounting for an average time to publication of almost two years.[7] Furthermore, of completed trials, only two have directly uploaded results to clinicaltrials.gov and none comply with CFR Part 11 Final Rule, which stipulates that the results and a copy of the final study protocol must be uploaded to clinicaltrails.gov within 1 year of the trial completion date.

Approximately two-thirds of registered trials are government, university or hospital funded, whilst one-third have been funded by industry or commercial sector organisations (Figure 3e). Concerningly, two trials have been patient funded and both of these are of unknown status (defined as no information being updated on clinicaltrials.gov for at least two years). Conversely, all industry funded trials have up-to-date information, and none are of unknown status. Of all trials that have been completed, there is a reasonably even split between funding sources. 33% of completed trials have been government funded, 39% hospital or university funded, and 28% industry funded. This suggests there is no significant predisposition in funding source for reaching the stage of trial registration, but

that some funding sources (e.g. industry) may promote more routine interim reporting. The majority of trials (84%) remain limited to a single-site and are not multicentre (Figure 3f).

Cell therapies used in SCI have been delivered using a variety of methods, ranging from injection directly into the spinal cord lesion epicentre to intravenous administration (Figure 4a). Most registered trials plan to deliver cells intrathecally, although approximately one-third are delivering cells either into the parenchyma of the spinal cord at or around the lesion site. Approximately a quarter of those delivering cells directly into the spinal cord lesion site have used cells in combination with biomaterial matrices, notably NeuroRegen Scaffold™ and RMx Biomatrix™.

Most trials are transplanting cells shortly after injury, with 31% delivering cells within one month of SCI (Figure 4b). A significant proportion of trials are also recruiting patients defined as having a stable baseline, although only one trial is explicitly recruiting more than two years after injury. Safety and adverse events are the primary outcomes for most ongoing trials, although predicted follow-up times are reasonably short. The majority of trials intend to monitor patients for a maximum of one or two years, with only a few trials extending follow-up beyond this period (Figure 4c). Interestingly, industry and government funded trials have the longest follow-up times. Approximately one-third of registered trials have or intend to incorporate rehabilitation after cell transplant, although the intensity and type of rehabilitation delivered is often not clearly specified (Figure 4d).

Published human studies by cell type

The mechanisms underlying repair after cell transplantation for SCI have been discussed in detail elsewhere,[8,9] and are also summarised in summarised in Table 1. A total of 37 cell therapy trials for SCI have been published in peer-reviewed journals, although a number of these are not corroborated with an accompanying national clinical trial (NCT) identifier from clinicaltrials.gov. Individual studies are summarised in **Table 2**, although it should be noted that some studies performed by similar research groups may display a degree of overlap and therefore the number of trials displayed in **Table 2** may overrepresent the number of truly unique cell therapy trials that have been published.

Neural stem cells

Five early stage published studies have used NSCs for non-penetrating, human traumatic SCI (**Table 2**). Four have used commercial NSC cell lines whilst the other used foetal tissue.[10-14] Compared to some other cell types, all five trials transplanted NSCs at reasonably high doses ($>10^7$ cells) via intramedullary injection, either directly into the lesion or into the perilesional spinal cord. No NSC trials have yet been sufficiently powered to determine efficacy, but four out of the five published examples have reported improvements in functional scores. NSC transplantation has also been reported to improve electromyography and electrophysiology.[11,14] No adverse effects have been reported so far,[14,17] even with reasonably long follow-up times of up to 60 months,[11,12] although longer follow-up studies are ongoing. However, the positive effects after NSC transplantation have not yet been corroborated with an improved quality of life for SCI patients.[11]

Mesenchymal stem cells

The majority of MSC studies have used cells derived from bone marrow,[15-25] although adipose tissue and umbilical cord MSCs have also been used (**Table 2**).[26-28] MSC trials have used wide inclusion criteria, often recruiting patients with a range of spinal injury levels. Combined with the heterogeneity in the classification and definition of MSCs,[29] this makes interpreting the effects of MSC transplantation challenging. Intrathecal MSC transplantation has been the most common delivery method, perhaps reflecting the hypothesised secretory and immunomodulatory effects of MSCs, rather than a mechanism of direct neural cell replacement within injured tissue.[30] Several MSC trials have also delivered cells repeatedly over multiple time points, increasing the cumulative number of cells transplanted.[15,18,20,22,28] Improvements following MSC transplantation have been variable, but the majority of trials delivering MSCs via an intramedullary or intrathecal route have reported encouraging results on function.[15,16,18,19,21,22,25,28] Most trials have not reported any adverse effects attributable to MSCs. However, one trial reported increased pain during the first 12 weeks after transplantation[15] and another the worsening of sensation in one patient.[26]

Mononuclear cells

Most MNC studies have used cells from either the bone marrow or blood,[31-39] although umbilical cord blood-derived MNCs have also been used (**Table 2**).[40,41] MNCs have been transplanted primarily either directly into the spinal cord parenchyma or intrathecally. Some trials have reported efficacious results,[31,33-35,37,38,40,41] yet others have reported no beneficial effect.[32,36] The largest studies, recruiting 277 and 297 patients, respectively, have indicated consistent improvements in American Spinal Injury Association (ASIA) grade.[35,42] Several trials have also highlighted that early transplantation (within six to twelve months of injury) may be essential for the efficacy of MNC transplantation.[31,42] Fever has commonly been reported,[35,38] yet it remains unclear whether this is attributable to

GM-CSF co-administration or MNC transplantation directly.[38] There have also been reports of pulmonary emboli and osteomyelitis, although these were deemed unlikely to be due to cell transplantation (**Table 2**).[34] One case study has performed repeated administration of MNCs intrathecally (up to 14 times) without adverse events.[41]

Schwann cells

Two published trials have used SCs for human spinal cord repair (**Table 2**). Both have used processed autologous sural nerve to produce purified primary human SC cultures. SCs were delivered into the lesion epicentre or surrounding spinal cord parenchyma. Anderson et al. did not report any adverse effects following SC transplantation,[43] yet Saberi et al. reported that all four patients in the trial experienced increased levels of paraesthesia and muscle spasm whilst only one patient saw improved motor function.[44] A separate study has explored the combined delivery of SCs with OECs, although only one patient received SCs alone, where positive effects were reported after transplantation.[45]

Olfactory ensheathing cells

All OEC trials have delivered cells directly into the spinal cord lesion site or surrounding tissue (**Table 2**). Two trials have used OECs derived and harvested from autologous olfactory mucosa,[46,47] whilst a single-patient case study has used autologous cells from the olfactory bulb combined with sural nerve bridges.[48] Chen et al. have also used foetal bulb OECs,[45] yet the largest OEC trial to date, recruiting 20 patients, used pieces of undissociated olfactory mucosal tissue.[49] The results from human OEC trials have so far been mixed. However, rehabilitation after transplantation may be essential for efficacy, with Lima et al. reporting a synergistic effect when OECs were transplanted together with a structured rehabilitation programme.[49]

Oligodendrocyte precursor cells

There are currently no published studies using OPCs, although one trial has recently completed recruitment for the primary outcome (NCT02302157). This is a commercially sponsored trial, using AST-OPC1 cells from Asterias Biotherapeutics, Inc. It is an open-label phase I/II design enrolling 25 patients and completed in December 2018. Unpublished interim data suggest that the majority of patients recruited have regained at least one motor level and there have been no reported serious adverse effects so far.[50] However, it should be highlighted that Asterias Biotherapeutics was founded after a previous Geron Corporation trial using the same cells was terminated prematurely on the basis of other commercial priorities. Termination occurred after patient recruitment had begun and subsequently ethical concerns were raised over the recruitment of vulnerable SCI patients and the early termination of cell therapy trials for commercial reasons.[51]

Remaining challenges for human SCI cell therapy trials

Significant challenges remain surrounding the use of cell therapies for SCI. Notably, the quality of trials remains highly variable. The majority of trials that are registered as completed are yet to generate any accompanying peer-reviewed publications. This is concerning as it may suggest trials with unfavourable outcomes or adverse events are not being appropriately reported or represented in the published literature. This reflects the conclusions of a recent *Lancet* commission, which highlighted reporting inconsistencies as a significant limitation of current regenerative medicine trials.[52] Under-reporting has been highlighted as a particular problem for clinical trials using stem cells to treat neurological disorders.[53] Indeed, regardless of whether the results are published,

regulators such as the FDA mandate that outcomes must be reported within 12 months of trial completion under Part 11 Final rule,[54] and low compliance within SCI cell therapy trials currently hinders shared learning opportunities, particularly in the area of safety. Including the unique NCT trial registration number in the CONSORT checklist at the time of submission for publication may also aid traceability and enable changes to trial design or outcomes to be tracked more robustly.[55]

Most cell therapy trials for SCI have not been prospectively registered. This goes against recommendations from the International Committee of Medical Journal Editors (ICMJE), which states that the results of cell and biological therapies should not be published without prospective registration.[56] Prospective registration is important for defining *a priori* endpoints, reducing selective outcome reporting and may also be associated with an increased likelihood of positive findings due to more robust trial planning.[57,58] Indeed, there have been numerous reports of off-shore commercial 'stem cell spas' using unlicensed cell therapy products.[59,60] The protocols and results of these treatments are not usually published in peer-reviewed journals, preventing scrutiny by field-specific experts and potentially leading to the exploitation of vulnerable patients. Such 'stem cell spas' may undermine legitimate cell therapy approaches. As for all medical research, informed consent, allocation blinding (e.g. for ASIA assessment) and externally reproducible preclinical studies are essential for transparent and robust reporting.

The heterogeneity of human SCI is also a significant challenge. SCI patients are a highly variable population and this has implications for trial recruitment.[61] For example, after complete cervical SCI up to 70% of patients may recover at least one spinal level one year after injury,[62] and up to 33% of patients with thoracic

injury ASIA A may convert to ASIA B or better.[63] This variability makes powering SCI trials problematic, particularly where many trials do not include an appropriate control group (e.g. patients receiving an identical sham procedure or rehabilitation programme but without cell transplantation). Consequently, reports of functional improvement (most commonly defined as the change in ASIA score from the start to the end of a study) in uncontrolled trials may be attributable to decompressive surgery at the time of cell transplantation or part of the natural history of SCI recovery.[64,65] Trials not appropriately powered for functional outcomes must be cautious about overinterpreting the perceived benefit of cell transplant. The Spinal Cord Outcomes Partnership Endeavours (SCOPE) provide excellent further resources on useful clinical outcome metrics (http://scope-sci.org/publications/). In the future, SCI trials may wish to move away from frequentist trial designs, instead utilising adaptive or Bayesian approaches that are increasingly favoured for drug discovery trials with small cohorts.[66]

Safety is also a fundamental concern for cell transplantation, particularly where progenitor cells or non-terminally differentiated cells are used. However, efficacy remains the primary focus of most preclinical experiments, despite an established safety profile being critical for the translation of any cell therapy into humans. Ectopic growth remains a major concern for SCI specifically,[67] owing to finite space within the spinal canal and the potential for cord compression. Indeed, the North American Clinical Trials Network ranks safety as the highest priority when assessing the translational potential of promising preclinical SCI therapies to first-in-human stage.[68] However, this is difficult to assess when a significant proportion of SCI trials are terminated prematurely, preventing long-term follow-up and robust safety assessment.[69] Such data are essential for calculating both the number needed to treat (NNT) and the number needed to harm (NNH). Both

parameters will be critical for assessing clinical effectiveness and performing cost-utility calculations.

The duration of follow-up after cell transplantation is another important consideration. The median reporting time for trials is currently 52 weeks. This may be insufficient to detect long-term adverse effects. Notably, several recent case reports have emphasised that long-term surveillance should be routine in all patients receiving cell therapy for SCI, where ectopic growth may take up to 8 years to manifest after transplantation.[70,71] This relates to the wider issue of transplant standardisation and establishing a robust set of 'release criteria' for each cell type prior to use in patients. More precise nomenclature and properly defined characterisation criteria are urgently required for many therapeutic cell types, but particularly for MSCs.[29,72] However, establishing robust release criteria for cell therapy products remains challenging, especially for autologous cell therapies.[73] Autologous cell products are subject to natural variability and are therefore inherently difficult to standardise. This may create difficulties in attaining the regulatory standards required for an advanced medicinal therapeutic product (ATMP). It is therefore encouraging where some regulatory frameworks have specified different criteria for autologous cell transplantation trials, taking into consideration the practical limitations of autograft testing, which cannot be as rigorous as usual pharmaceutical standards, but without compromising patient safety. The regulation of cell therapies vary greatly between different countries,[74,75] and increased regulatory harmonisation may help accelerate clinical translation.[76]

Better understanding the mechanisms that underpin how specific cell types facilitate recovery after SCI would also increase the likelihood of cell therapies progressing to late-stage clinical trials. For novel pharmaceuticals, drugs are

routinely assessed against the 'three pillars' of drug development – pharmacodynamics, pharmacokinetics and toxicity.[77] Thoroughly understanding how new compounds perform in relation to each of these is highly predictive of progression to phase III trials and future licensing.[78,79] Cell therapies clearly differ from drug compounds, yet robust dosing studies are often neglected in cell therapy trials and preceding preclinical studies, although they are likely to be essential for optimising efficacy. An improved understanding of the mechanisms that underpin repair for specific cell types could enable more focused delivery approaches.[8] This may reduce the need for combined delivery routes, facilitating easier trial logistics and minimising the variability in small patient cohorts. The lack of predictive biomarkers, both in clinical studies and pre-clinical models, is currently one of the greatest challenges for SCI research overall.[80,81]

The role of rehabilitation must also be carefully considered in the design of SCI cell therapy trials. Delivering cells in isolation removes the risk of rehabilitation as a confounder, yet it may also limit activity-dependent plasticity changes that underpin repair by some therapeutic cells.[82,83] This is especially true where increased neuroplasticity is hypothesised as a central mechanism of action. Indeed, one trial using OECs has concluded that adjunctive rehabilitation was essential for functional recovery.[49] Consequently, where rehabilitation is provided it should be delivered as part of a standardised intervention programme so that individual patient adherence can be closely monitored and correlated with outcomes.

Poor cell survival after transplantation is a fundamental issue for most cell therapies in SCI.[84-86] Minimising cell death could increase the potency of transplants and may be critical for improving autologous therapies, where there is often a limited amount of starting tissue. Within preclinical research, spinal cord

repair strategies are moving away from simple cell-only injections and beginning to explore therapeutic approaches where cells are delivered in combination with biomaterials. Biomaterials may aid cell survival and they also provide important structural support for both transplanted cells and regenerating host tissue.[87] To date, very few trials have explored biomaterial approaches to enhance cell delivery. Future trials may wish to focus on utilising realistic and scalable tissue engineering technologies that enhance cell delivery, optimise cell survival and facilitate improved functional recovery.[88] However, specific challenges for the delivery of biomaterials into the spinal cord will need to be considered. These have been reviewed in detail elsewhere,[88-90] but may include the need for minimally-invasive delivery methods, in situ gelation, appropriate biomaterial degradation rate, suitable mechanical properties for interface with spinal cord tissue and self-assembly within the spinal cord lesion site.[91,92].

SCI researchers may also wish to reflect on other areas where cell therapies have been used to treat neurological disorders. For example, in Parkinson's disease induced pluripotent stem cells (iPSCs) have rapidly advanced towards first-in-human testing and are now undergoing clinical trials in Japan. This has been underpinned by the use of non-human primate models to determine efficacy and consideration of practical challenges such as human leukocyte antigen (HLA) matching for allogenic transplant.[93,94] The Parkinson's disease cell therapy community have been at the forefront of establishing large, multicentre collaborative initiatives (such as TRANSEURO) and these have established the infrastructure required to perform large-scale cell therapy trials.[95] Multiple sclerosis has also seen a number of completed cell therapy studies,[96,97] which have included dose-escalation and follow-up as long as 5 years.[98,99] Equivalent collaborative initiatives are likely to be necessary for running adequately powered SCI trials in the future. Multinational consortia may also help to secure

sustainable funding and ensure cost-effective scale-up of cell manufacturing facilities and recruitment sites. Collaborative initiatives are beginning to gain traction for SCI, including the North American SCI Consortium, EuroStemCell and ChinaSCINet,[100] and these will be essential for facilitating robust trials in the future.

Conclusions and future directions:

A range of cell therapies have now reached early clinical trials for the treatment of SCI. There has been a global effort to translate exciting preclinical advances to patients; however, the lack of prospective trial registration, inconsistent reporting and cell characterisation remain significant challenges. Cell therapies for SCI are now at a tipping point. Current phase I and II trials will ultimately determine whether further phase III trials will be funded. These will be essential for future licensing and potentially changing the routine clinical management of SCI. Despite the wave of enthusiasm for cellular therapies over the past decade, we are now starting to appreciate the difficulties in controlling cell behaviour and the characterisation of biological medicinal products. If cell therapies are to have a significant impact on the treatment of SCI in the future, methodological and regulatory inconsistencies must be overcome, together with enhanced funding to facilitate appropriately powered, multi-centre, consortium-led and phase III clinical trials. The SCI research community must now come together and work collaboratively to generate the practice-changing trials of the future that are so desperately required to improve the management of SCI.
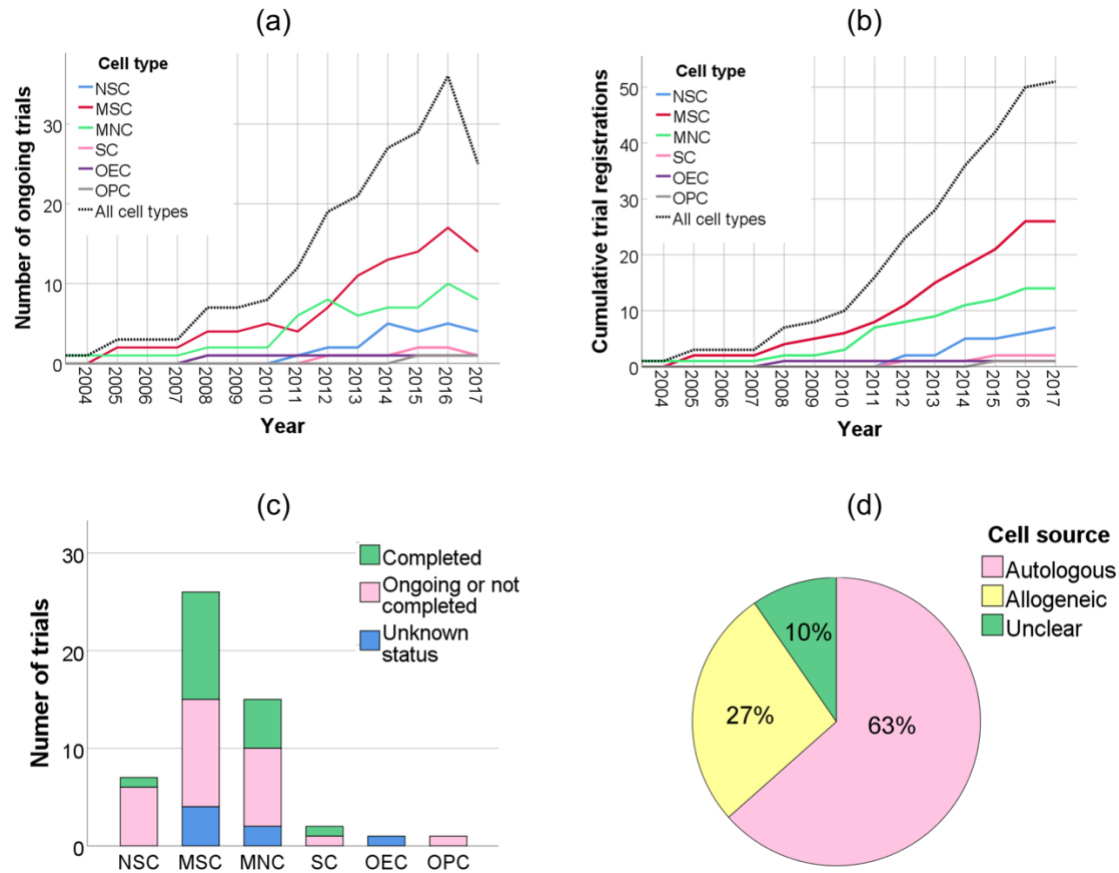
Figure 1. Emerging cell therapies for human spinal cord injury. (a) Number of ongoing trials by cell type over time; (b) cumulative number of trial registrations by cell type over time; (c) completion status of trials for each cell type; (d) source of cells used in trials. NSC - neural stem cell; MSC - mesenchymal stem cell; MNC - mononuclear progenitor cell, SC - Schwann cell; OEC - olfactory ensheathing cell; OPC - oligodendrocyte precursor cells. High resolution – link.
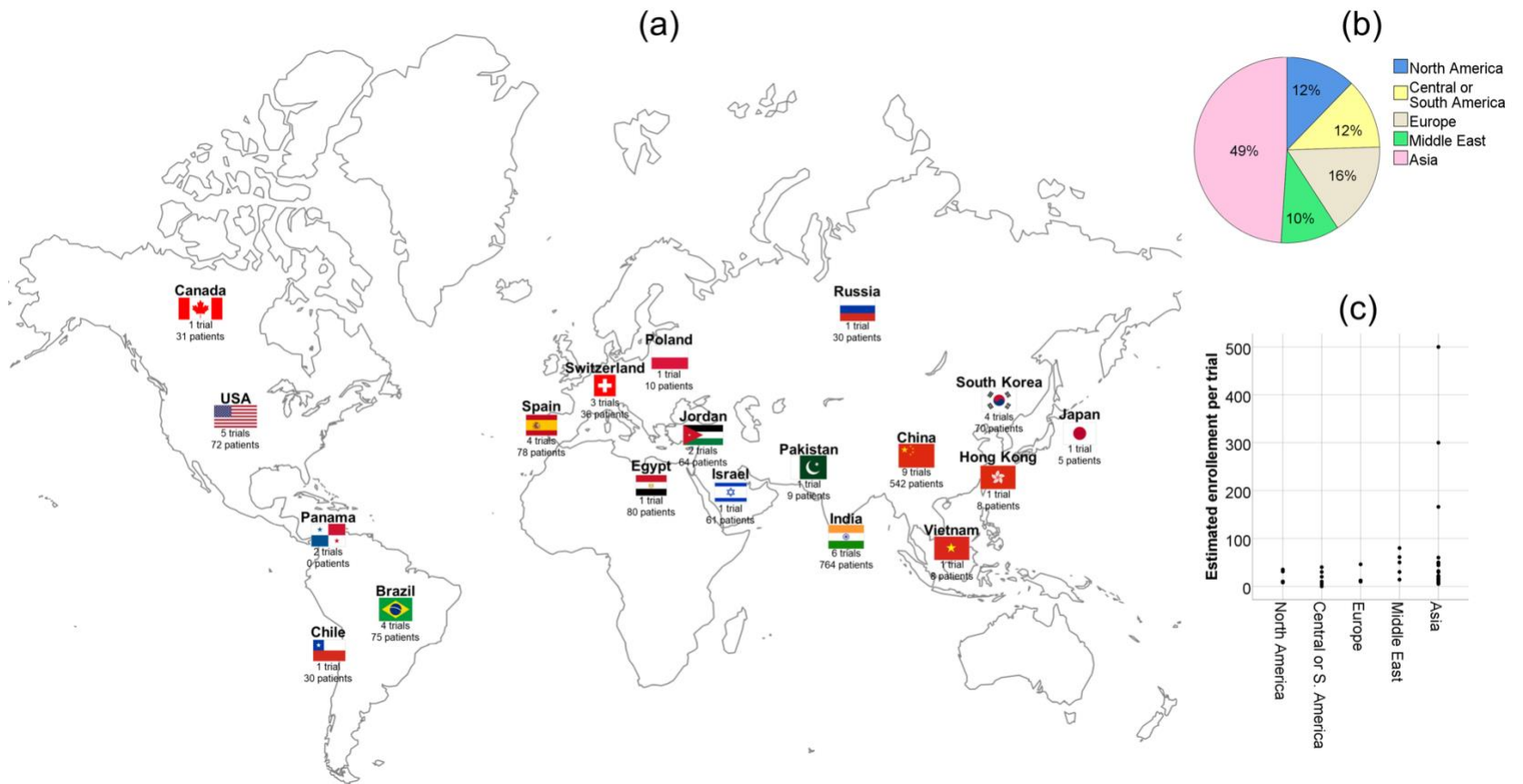
Figure 2. Global distribution of all registered trials using cell therapies for SCI. (a) Number of trials and patients registered per country; (b) summary of proportion of trials by geographical region; (c) estimated enrolment by geographical region. High resolution - link.
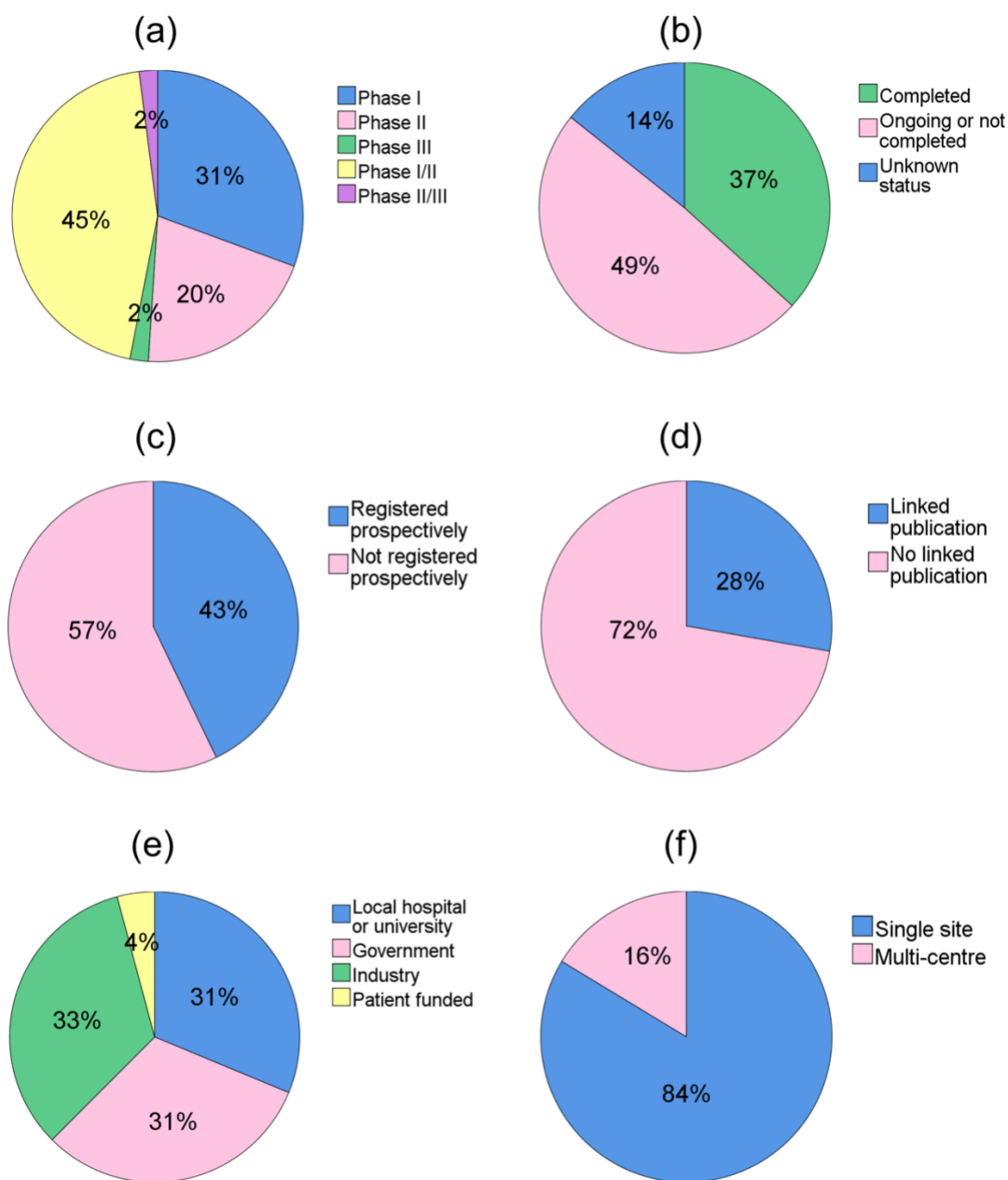
Figure 3. Current demographics of cell therapy trials for SCI. (a) Stage of testing; (b) trial completion status; (c) time of registration on clinicaltrials.gov; (d) proportion of completed trials with accompanying publication; (e) source of funding; (f) number of recruitment sites. High resolution – link.

Figure 4. Summary of outcomes for human cell therapy trials for SCI. (a) Location of cell delivery; (b) earliest time after injury patients are eligible for cell transplant, (c) duration of clinical follow-up; (d) proportion of trials using rehabilitation. High resolution – link.

Table 1. Overview of therapeutic cell types currently being used for human SCI.

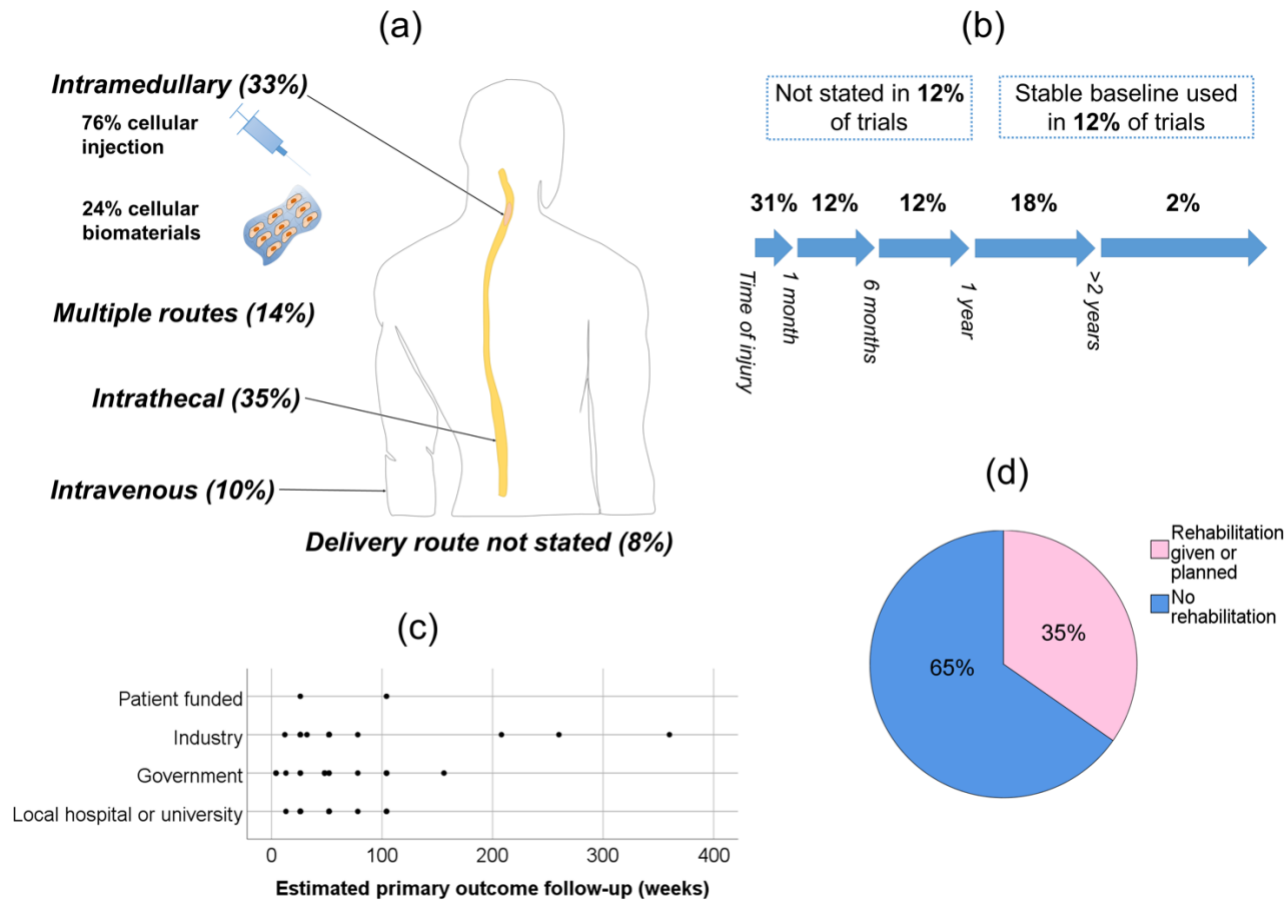| Cell type	Likely mechanism in spinal cord repair	Additional information
NSCs	Synapse with host neurons to reconstitute neural connections.	• Self-renewing, multipotent cells with the potential to differentiate into neurons and glia.[101] • Able to extend hundreds of thousands of axons over multiple spinal levels in non-human primate models of SCI.[3,102] • Able to synapse on neurons in host grey matter and facilitate restoration of ascending and descending fibre tracts.[103] • Aim to reconstitute neural connections within the damaged spinal cord.
MSCs	Neuroprotection and immunomodulation	• Multipotent stromal cells harvested from a variety of sources, including bone marrow, adipose tissue and umbilical cord.[104] • Characteristics of exactly how MSCs are defined remains controversial.[29] • Likely to act through a variety of mechanisms, but secreted factors neuroprotective factors and immunomodulatory effects are likely to be important mechanistically.[105,106]
MNCs	Not well characterised.[107,108]	• MNCs are isolated from bone marrow aspirate or blood, typically after stimulation with granulocyte-macrophage colony-stimulating factor (GM-CSF).[109] • Likely to secrete a range of factors,[110] including VEGF and BDNF. [111], which may induce vascularisation, transdifferentiation, or local modulation of the lesion site.[108,112] • Unlike other cells, MNCs do not typically require prolonged culture periods and they can often be transplanted following only minimal manipulation (e.g. cell sorting and centrifugation).[113]
SCs	Secretion of growth promoting factors, cell	• Resident glial cells of the peripheral nervous system

	guidance for axon regeneration, myelination.[1]	• Responsible for the successful repair and remyelination of axons following peripheral nerve injury.[114,115] • Due to the intrinsic repair after peripheral nerve injury,[116,117] it is hypothesised that SC transplant may be able to create a pro-regenerative environment at the SCI lesion site.[116,117]
OECs	Secretion of neurotrophic factors,[118] modulation of astrocyte activity,[119] remyelination of large diameter axons,[120] key cell-cell guidance cues required for successful regeneration.[121]	• Specialised population of glia that reside in the olfactory epithelium of the nose and olfactory bulb of the brain. • Responsible for maintaining and regenerating the sensory olfactory nerves throughout normal adult life (neurogenesis).[122] • Can be harvested safely using minimally invasive endoscopic surgery,[123] making them an attractive prospect for autologous cell therapy. • Display a variety of useful behaviours, but particularly 'pathfinding' through reactive astrocytes and direct cell-cell guidance of neurons.[124]
OPCs	Reconstitution of host CNS tissue and myelination	• Compose approximately 5-8% of endogenous cells within the central nervous system.[125] • May differentiate into myelinating oligodendrocytes, but also neurons and astrocytes.[126] • May be able to differentiate to reconstitute host CNS tissue and also facilitate myelination after SCI.[127]

Table 2. Published clinical trials using cell therapies for SCI. Abbreviations: electromyography (EMG), international standards for neurological classification of spinal cord injury (ISNCSCI), brain motor control assessment (BMCA), quality of life (QoL), graded redefined assessment of strength, sensibility and prehension (GRASSP), American Spinal Injury Association (ASIA).

Study	Cell type	Cell source	Dose	Delivery method	Number of patients	Injury region	Trial design	Outcomes of interest	Rehabilitation regime	Adverse response monitoring	Main findings
Curtis *et al.* 2018 [11]	NSC	NSI-566 (Neuralstem, Inc.)	1×10^8 cells	Intramedullary	4	Thoracic	Phase I (single-blinded)	Safety monitoring, including surgery-related complications, increased spontaneous or evoked pain, and MRI changes	Routine outpatient physical therapy	Up to 60 months	No major adverse events. Improvements to EMG. ISNCSCI and BMCA scores improved, but no significant improvements to QoL
Ghobrial *et al.* 2017 [10]		huCNS-SC (Stem Cells, Inc.)	4×10^7 cells	Intramedullary	5	C5 - C7	Phase II (single-blinded, randomised)	Functional recovery	Not specified	Not specified, but reported previously for cell type	Some improvements in GRASSP and ISNCSCI scores
Levi *et al.i* 2018 [12]		huCNS-SC (Stem Cells, Inc.)	Up to 4×10^7 cells	Intramedullary	29	Cervical (n = 17), thoracic (n = 12)	Phase I/II dose escalation (single-blinded, randomised)	Safety and feasibility	Not specified	Up to 56 months	Delivery of up to 4×10^7 cells using manual injection method appeared feasible and safe
Levi *et al.* 2019 [13]		huCNS-SC (Stem Cells, Inc.)	Up to 4×10^7 cells	Intramedullary	16	Cervical	Phase II (single-blinded, randomised)	Functional recovery, spasticity and allodynia	Not specified	12 months	Improvements in GRASSP and UEMS score, but trial terminated prematurely due to *a priori* futility analysis
Shin *et al.* 2015 [14]		Foetal telencephalon	1×10^8 cells	Intramedullary	19	C3 - C8	Phase I/II (open-label, non-randomised)	Functional recovery, electrophysiology and MRI	Not specified	12 months	Modest improvements to ASIA score. Early transplant associated with improved outcomes

Study	Cell type	Source	Dose	Route	N	Level	Study type	Outcomes measured	Rehabilitation	Follow-up	Results
El-Kheir *et al.* 2014 [15]			Cumulative target of 2×10^6 cells/kg spread over four injections, each one month apart	Intrathecal	70	Thoracic or cervical	Phase I/II (single-blinded, randomised)	Long-term safety, functional improvement and improvement in motor score	At least 1-2 hours three times per week, matched for control and intervention groups	18 months	17/50 patients in the cell transplant group saw improvements in ASIA classification; some patients receiving cell therapy noted transient increases in pain during the first 12 weeks after transplant
Mendonca *et al.* 2014 [16]			5×10^6 cells per cm^3 lesioned tissue	Intramedullary	14	Thoracic or lumbar	Phase I (uncontrolled)	Functional recovery, pain, electrophysiology and MRI	5 times per week for 6 months. 4 hours a day for the first 2 months post-operatively and then 2 hours per day in subsequent months	6 months	Improvement in ASIA score in 7/14 patients
Moviglia *et al.* 2009 [23]	MSC	Bone marrow	Not specified	Intravenous	8	Cervical	Case report	Functional recovery and MRI	Not specified	30 months	Some patients saw functional or radiographic improvements
Garcia-Olmo *et al.* 2018 [24]			Cumulative dose of 3×10^8 cells, delivered as three 1×10^8 cell injections at 3 month intervals	Intrathecal	1	L1	Case report	Bowel dysfunction and MRI	Not specified	Not specified	Improvements in anal squeeze pressure, MRI and neurogenic bowel dysfunction score.
Pal *et al.* 2009 [17]			1×10^6 cells/kg	Intrathecal	30	Cervical or thoracic	Phase I (uncontrolled)	Feasibility, safety and activity scores	Not specified	36 months	No adverse effects reported up to 3-year follow-up
Park *et al.* 2012 [18]			8×10^6 cells intramedullary, plus 4×10^7 cells intrathecal. Further 5×10^7 cells delivered intrathecally	Intramedullary and intrathecal, plus delayed intrathecal	10	Cervical	Phase I (uncontrolled)	Motor score, activities of daily living, MRI,	No rehabilitation programme delivered before or after cell therapy	36 months	6/10 patients showed changes to motor score and three of these also saw improvements to QoL; no adverse effects reported

Study	Cell type	Dose	Delivery	n	Injury level	Study type	Outcomes measured	Rehabilitation	Follow-up	Results
										at 4 and 8 weeks.
Saito et al. 2012 [19]		$3 - 5 \times 10^7$ cells	Intrathecal	5	C4 - C6	Phase I/II (open-label, non-randomised)	Adverse events and MRI	Not specified	6 months	Improvements in patients with ASIA B or C, but limited recovery in patients with ASIA A. No adverse effects reported
Satti et al. 2016 [20]		Median 1.2×10^6 cells/kg spread over two to three injections	Intrathecal	9	Thoracic	Phase I	Adverse events	Not specified	12 months	Good-manufacturing practice production of cells feasible and no adverse effects reported
Vanquero et al. 2016 [21]		$1.0 - 2.3 \times 10^8$ cells into the spinal cord, plus a further 3×10^7 cells at 3 months intrathecally	Intramedullary, plus delayed intrathecal	12	Thoracic	Phase I/II	Adverse events, functional recovery, pain, spasticity, bladder function, electrophysiology, urodynamics, MRI	Not specified	12 months	Improvements in sensitivity, sphincter control and sexual function, decreased spasticity and improvements to motor function
Vanquero et al. 2017 [22]		Four doses of 3×10^7 cells	Repeated intrathecal	12	Cervical, thoracic and lumbar	Phase II	Functional recovery, pain, spasticity, bladder and bowel function	Not specified	12 months	Improvements to pin prick, light touch sensation, motor score and ASIA grade
Derakhshanrad et al. 2015 [25]		4.1×10^7 cells	Intrathecal	1	T12	Case report (blinded analysis)	Functional recovery, kinematic gait analysis, pain, MRI, adverse events	6 sessions per week for 6 months	12 months	Patient converted from ASIA A to C
Hur et al. 2016 [26]	Adipose-derived	9×10^7 cells	Intrathecal	14	Cervical, thoracic and lumbar	Phase I (single-blinded)	Adverse events, electrophysiology, MRI, functional scores	No specific rehabilitation provided	8 months	ASIA motor scores improved in 5/14; voluntary anal contraction 2/14; sensory recovery in 10/14. One patient saw worsening of sensation, others reported headache, nausea and vomiting

Study		Cell source	Cell number	Route	N	Level	Phase	Outcomes	Control	Follow-up	Results
Ra et al. 2011 [27]			4 x 10^8 cells	Intravenous	8	Not clearly stated	Phase I	Adverse events,	Not specified	3 months	One patient improved from ASIA A to C. No adverse events at 3 months
Cheng et al. 2014 [28]		Umbilical cord	Two transplants of 2 x 10^7 cells, with second transplant delivered 10 days after the first.	Repeated intramedullary	34	T10 - L1	Phase I (controlled)	Functional recovery, adverse events, urodynamics,	Not specified, but control and rehabilitation only groups used as controls	12 months	7/10 patients in cell therapy group saw improvements in motor scores, self-care and muscular tension; 5/14 saw improvements following rehabilitation only without cell therapy. Cell therapy group also had improved urodynamics
Bansal et al. 2016 [31]		Bone marrow	Cell number dependent on yield from aspirate; three transplants, each separated by four weeks	Intrathecal	10	Cervical or thoracic	Phase I	Functional recovery, posture, gait, urodynamics, sexual function, spasticity, MRI	Standard local rehabilitation protocol	12 months	6/10 patients showed improvements in ASIA grade; the effect of cell transplantation was greater when transplanted < 6 months after injury
Chhabra et al. 2016 [32]	MNC	Bone marrow	2 x 10^8 cells injected into the spinal cord, or 2 x 10^8 cells delivered intrathecally	Intramedullary or intrathecal	21	T1 - T12	Phase I/II (single-blinded, randomised)	Functional recovery, electrophysiology, spasticity, urodynamics, patient reported outcome measures, depression score	Standardised local rehabilitation programme, although details not specified	12 months	No adverse safety events, but no efficacy attributable to cell transplantation
Deda et al. 2008 [33]		Bone marrow	2.0 - 6.7 x 10^7 cells depending on patient yield	Intramedullary, intrathecal and intravenous	9	C3 - T11	Case series	Functional recovery, adverse events, MRI, electrophysiology,	All patients had undergone rehabilitation prior to cell transplant, but details of post-operative rehabilitation programme not specified	12 months	Improvements in ASIA grade; no adverse effects reported

Hammadi *et al.* 2012 [42]		Blood	1 - 8 x 10^8 cells	Intrathecal	277	Cervical and thoracic	Not specified.	Functional recovery	Not specified	12 months	120/277 (43.3%) patients saw clinical improvements within 4 weeks after starting therapy. 88/277 (31.8%) converted from ASIA A to B, and 32/277 (11.6%) converted from ASIA A to C. Patients who received transplant within 1 year of SCI had the best outcomes.
Kumar *et al.* 2009 [35]		Bone marrow	3.66 - 4·20 x 10^8 cells	Intrathecal	297	Cervical and thoracic	Phase I/II (open-label, non-randomised)	Functional recovery, safety and therapeutic time window	Not specified	3 months	97/297 patients showed improvements in ASIA grade. Potential adverse effects including fever, headache and tingling
Lammertse *et al.* 2012 [36]		Blood and skin	1.5 x 10^6 cells	Intramedullary	43	C5 - T11	Phase II (single-blinded, randomised)	Functional recovery, independence measures, quality of life	Performed per 'Outcomes Following Traumatic Spinal Cord Injury' guidelines published by the Consortium for Spinal Cord Medicine Clinical Practice	12 months	No significant improvement in ASIA score due to cell therapy
Sharma *et al.* 2012 [37]		Bone marrow	1 x 10^6 cells/kg intrathecal plus intramuscular	Intrathecal and intramuscular	4	Not clearly stated	Not specified	Nerve conduction studies, muscle strength, urodynamics, sitting balance, sensation, muscle tone	Between 6 and 12 months based on individual neurorehabilitation plans formulated for each patient prior to cell delivery	15 months	3/4 paediatric patients had improvements in muscle strength or urinary continence; 2/4 had improvements in sensation or spasticity reduction
Sharma *et al.* 2014 [39]		Bone marrow	Two injections of 8.3 x 10^7 cells	Intrathecal	1 (paediatric)	C7-T1	Case study	Functional outcomes,	Performed but details not specified	6 months	Improved urinary control and gait. Also improvements in sensation to lower limbs.

			six months apart				urodynamics, sensory, gait			ASIA grade remained unchanged
Yoon et al. 2007 [38]		Bone marrow	2×10^8 cells transplanted either at <14 days, between 14 days and 8 weeks, or >8 weeks after injury	Intramedullary	35	Not clearly stated	Phase I/II (open-label, blinded observer, non-randomised)	Functional recovery, pain, safety, MRI	Not specified, but control group received equivalent rehabilitation to cell therapy group	10 months	Cell transplant during the acute or subacute phases after injury improved outcomes compared to cells transplanted at >8 weeks. 22/35 patients in treatment group had fevers, possibly attributable to GM-CSF or cell administration
Ichim et al. 2010 [41]		Umbilical cord	14 combined cell doses over an 8-month period, with each dose consisting of 1.5 - 3.0 x 10⁶ CD34+ve cells and 3.9 - 7.0 x 10⁶+ MSCs	Intrathecal	1	T12	Case study	Functional recovery, safety, pain, urodynamics, bowel function	At least 4 weeks of dedicated rehabilitation in in patient facility	36 months	Improvements in pain, bowel and bladder function, and transition from ASIA C to D
Zhu et al. 2016 [40]		Umbilical cord	Either 1.6 x 10⁶, 3.2 x 10⁶, 6.4 x 10⁶ cells or 6.4 x 10⁶ cells plus methylprednisolone	Intramedullary	28	C5 - T11	Phase I/II	Adverse events, functional recovery, pain, , spasticity, bowel and bladder function, walking, independence measures	Not specified	12 months	Improvements in locomotor scores and bowel and bladder function when cell transplant combined with rehabilitation training. Future randomised trials planned
Anderson et al. 2017 [43]	SC	Processed autologous sural nerve	Dose-ranging up to a maximum of 1.5 x 10⁷ cells	Intramedullary	9	T1 - T6	Phase I (open-label, non-randomised)	Adverse events, MRI, pain, spasticity	Rehabilitation as per standardised local care, prescribed individually for each patient	12 months	Autologous harvest and purification of sural nerve Schwann cells feasible; no reported adverse events
Saberi et al. 2008 [44]		Processed autologous sural nerve	3.0 - 4·5 x 10⁶ cells	Intramedullary	4	Thoracic	Case series	Adverse events, functional recovery, sphincter tone,	Supervised rehabilitation started 6	12 months	One patient saw improvements in motor and sensory scores; 4/4 patients reported increased

Study		Cell source	Dose	Delivery	n	Injury level	Study design	Outcome measures	Rehabilitation	Follow-up	Results
								sexual function, MRI, spasticity	months prior to cell transplant		paraesthesia and muscle spasm after transplantation
Chen *et al.* 2014 [45]		Primarily foetal olfactory bulb (although other patients received Schwann cells or OECS plus Schwann cells)	1 x 10^6 cells	Intramedullary	3	C4 - C7	Phase I (double-blinded, randomised)	Functional recovery, EMG, electrophysiology	6 months rehabilitation programme	12 months	All patients saw improvements in muscle strength and EMG
Feron *et al.* 2005 [46]		Processed autologous olfactory mucosal cells	1.2 x 10^7, 2.4 x 10^7 or 2.6 x 10^7 cells	Intramedullary	3	T4 - T10	Phase I (single-blinded, controlled)	Functional recovery, MRI, feasibility and characterisation of human OEC cultures	Not specified	36 months	No adverse effects reported at 1-year follow-up
Lima *et al.* 2010 [49]	OEC	Unprocessed autologous olfactory mucosal tissue	N/A tissue explants	Intramedullary	20	Cervical or thoracic	Phase I/II (open-label, non-randomised)	Functional recovery, sphincter control, anal sensation, urodynamics, independence measures, walking	Pre-operative rehabilitation of mean 32 hours per week for 30 weeks and post-operative rehabilitation of mean 33 hours per week for 92 weeks. Included overground walking and brain-initiated non-robotic/non-weight support training	28 months	Improvements in ASIA grade in 11/20 patients, along with 15/20 showing improved EMG. Cells alone or rehabilitation alone were unlikely to be sufficient for functional recovery; a combination of both were required for benefit
Mackay-Sim *et al.* 2008 [47]		Processed autologous olfactory mucosal cells	Not clearly stated	Intramedullary	6	T4 - T10	Phase I/II (single-blinded, controlled, non-randomised)	Adverse events, functional recovery, independence measures, MRI	Not performed as primary outcome was safety of cell transplantation	36 months	No functional improvements or neuropathic pain; no adverse events reported within 3-year follow-up

Tabakow *et al.* 2013 [48]		Autologous olfactory bulb cells and sural nerve	5×10^5	Intramedullary	1	T9	Case study	Functional recovery, adverse events, independence, psychological assessment, MRI, electrophysiology, EMG, urodynamics	8 months of intensive preoperative rehabilitation (no change from baseline), followed by 19 month post-operative rehabilitation programme	19 months	Procedure feasible and efficacious when cell transplant combined with rehabilitation

Supplementary Information - search strategy and selection criteria

A comprehensive search of the clincaltrials.gov database was performed using the following search criteria "spinal cord injuries" and "cell OR stem OR regen* OR tissue engineer*" on 26/09/2018. A total of 199 results were returned, all of which were then manually screened by title. 49 registered trials were deemed relevant as using cell therapies for spinal cord injury. Information about each trial was manually extracted and collated. Analysis was performed using IBM SPSS Statistics 23.0. PubMed articles that linked from clincaltrials.gov were followed-up for additional information where appropriate. Completed trials were also manually searched using the unique trial identifier. Further PubMed searches were also performed using the terms "spinal cord OR SCI" and "neural stem cell* or NSC*", "mesenchymal cell* or MSC*", "mononuclear precursor cell* or MNC*", "Schwann cell* or SC", "olfactory ensheathing or olfactory glia* or OEC*" or "oligodendrocyte precursor* or OPC*". Article type was then restricted to 'clinical trial' to identify any further published studies that had not been registered on clinicaltrials.gov. Additional searches were performed to identify case studies where appropriate.

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