Neurobiology of Disease 62 (2014) 338–353

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Mesenchymal stem cells improve locomotor recovery in traumatic spinal cord injury: Systematic review with meta-analyses of rat models

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ARTICLE INFO

Article history:
Received 2 July 2013
Revised 13 September 2013
Accepted 10 October 2013
Available online 19 October 2013

Keywords:
Traumatic spinal cord injury
Locomotor recovery
Mesenchymal stem cells
Meta-analysis
Systematic review

ABSTRACT

Traumatic spinal cord injury (SCI) is a devastating event with huge personal and societal costs. A limited number of treatments exist to ameliorate the progressive secondary damage that rapidly follows the primary mechanical impact. Mesenchymal stem or stromal cells (MSCs) have anti-inflammatory and neuroprotective effects and may thus reduce secondary damage after administration. We performed a systematic review with quantitative syntheses to assess the evidence of MSCs versus controls for locomotor recovery in rat models of traumatic SCI, and identified 83 eligible controlled studies comprising a total of 1,568 rats. Between-study heterogeneity was large. Fifty-three studies (64%) were reported as randomised, but only four reported adequate methodologies for randomisation. Forty-eight studies (58%) reported the use of a blinded outcome assessment. A random-effects meta-analysis yielded a difference in behavioural Basso–Beattie–Bresnahan (BBB) locomotor score means of 3.9 (95% confidence interval [CI] 3.2 to 4.7; $P < 0.001$) in favour of MSCs. Trial sequential analysis confirmed the findings of the meta-analyses with the upper monitoring boundary for benefit being crossed by the cumulative Z-curve before reaching the diversity-adjusted required information size. Only time from intervention to last follow-up remained statistically significant after adjustment using multivariate random-effects meta-regression modelling. Lack of other demonstrable explanatory variables could be due to insufficient meta-analytic study power. MSCs would seem to demonstrate a substantial beneficial effect on locomotor recovery in a widely-used animal model of traumatic SCI. However, the animal results should be interpreted with caution concerning the internal and external validity of the studies in relation to the design of future clinical trials.

Introduction

Spinal cord injury

Traumatic spinal cord injury (SCI) is a catastrophic and disabling event that results in severe motor, sensory, and autonomic dysfunction. The costs of SCI are enormous for the affected individual with a significant impact on quality of life and life expectancy (Boakye et al., 2012; Devivo, 2012; Geyh et al., 2013; Middleton et al., 2012). Almost 50% of all traumatic SCIs result in complete loss of function below the level of injury and the cost of medical care for the first year for a patient with high tetraplegia is estimated at $800,000 and for a patient with paraplegia at $300,000. Accordingly, if a person sustains a SCI at the age of 25, lifetime medical costs would surpass $3.3 million in the case of high tetraplegia and $1.1 million for paraplegia. Worldwide, 2.5 million people are affected with SCI, and every year more than 130,000 people sustain a traumatic SCI (Adams and Cavanagh, 2004). In addition, as many are estimated to contract a non-traumatic spinal cord lesion although the available data in many areas of the world are lacking (New et al., in press; Noonan et al., 2012).

In traumatic SCI, the primary damage refers to the mechanical impact that within seconds to minutes leads to a disrupted blood–brain-barrier, haemorrhages, disrupted axons, and broken neural-cell body membranes. A broad spectrum of progressive secondary damage soon follows (minutes to weeks), consisting of ischaemia, oedema, biochemical changes, and inflammatory cell responses that substantially aggravate the primary injury in rostro-caudal direction, thus affecting subsequent neural repair and regeneration (Hausmann, 2003; Oyinbo, 2011). Detrimental biochemical changes include excessive calcium influx-mediated neuron and glial apoptosis, glutamate excitotoxicity, lipid peroxidation, and nitrous oxide excess. Main inflammatory effector cells

Abbreviations: α, risk of type I error; β, risk of type II error; BBB, Basso–Beattie–Bresnahan; CI, confidence interval; CSPGs, chondroitin sulphate proteoglycans; D2, diversity; I2, inconsistency measure; IFNγ, interferon gamma; lacZ, betagalactosidase; M1, classically activated macrophage/microglia; M2, alternatively activated macrophage/microglia; MAG, myelin-associated glycoprotein; MOG, myelin oligodendrocyte glycoprotein; MSC, mesenchymal stem cell; Nogo-A, neurite outgrowth inhibitor A; SCI, spinal cord injury; SD, standard deviation; SE, standard error; TSA, trial sequential analysis.

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http://dx.doi.org/10.1016/j.nbd.2013.10.014

comprise waves of activated neutrophils and classically activated (M1) blood borne macrophages and tissue-resident microglia (Beck et al., 2010; Fleming et al., 2006) which are associated with the rapid increase in neurotoxic matrix metalloproteinases, reactive oxygen species, and pro-inflammatory cytokines (Fleming et al., 2006; Nguyen et al., 2007; Noble et al., 2002).

Later, in the chronic phase, the spinal cord is characterised by continuing white-matter demyelinisation, atrophy, Wallerian degeneration, and central cavity formation in previously injured areas. Eventually, a developing glial scar is characterised by reactive astrocytes, activated resident microglia, invading macrophages, and potent neurite growth-inhibiting substances such as chondroitin sulphate proteoglycans (CSPGs), myelin-associated glycoprotein (MAG), myelin oligodendrocyte glycoprotein (MOG), and neurite outgrowth inhibitor (Nogo)-A (Bregman et al., 1995; Filbin, 2003; Freund et al., 2006).

In a contusion lesion, which is the most common morphological type of injury, the amount of primary macerated nervous tissue is relatively low. Instead, progressive secondary damage is more predominant, which in time may encompass several spinal segments above and below the original impact, thus extending the functional impairment. Especially the post-traumatic neuroinflammatory response is thought to be one of the most important mediators herein (Trivedi et al., 2006).

Current best available care of SCI traumas includes early surgical intervention, hypertensive therapy with vasoactive agents, and methylprednisolone derivates, and future treatment modalities may consist of promising early phase agents such as minocycline, Cethrin™, and riluzole (Breslin and Agrawal, 2012; Cadotte and Fehlings, 2011; Hawryluk et al., 2008; Kwon et al., 2011a; Kwon et al., 2011b; Tator et al., 2012).

Mesenchymal stem cells

In the absence of full recovery for many cell degenerative disorders, stem cells may hold promise as a novel treatment modality (Donnelly et al., 2012; Sahni and Kessler, 2010). Accordingly, more than 2700 clinical cell therapy trials have been initiated during the first decade of the 21st century (Culme-Seymour et al., 2012). Stem cells are a heterogeneous group of cells, but share the unique feature of being able to self-renew as well as differentiate into more specialised cells by means of asymmetric cell division (Oliveri, 2007). Multipotent mesenchymal stem cells (MSCs) are currently occupying centre stage in preclinical and clinical stem cell research due to their plethora of regenerative effects together with their relative ease of isolation, efficient ex vivo expansion, lack of ethical concerns, and acceptable safety profile (Lalu et al., 2012; Prockop et al., 2010; Singer and Caplan, 2011; Uccelli et al., 2008; von Bahr et al., 2012). Thus, human MSCs have shown promising results in a number of diverse clinical conditions such as graft-versus-host disease (Le Blanc et al., 2008), Crohn's disease (Duijvestein et al., 2010), adjuvant induction therapy in organ transplantation (Tan et al., 2012), and ischaemic cardiomyopathy (Hare et al., 2012). MSC-like cells can be isolated from tissues such as bone marrow, adipose tissue and umbilical cord, where they are believed to reside in the perivascular niches and play a pivotal role in local tissue homeostasis (Crisan et al., 2008). Besides having intrinsic mesodermal differentiation capabilities, MSCs have more recently also shown to exhibit other coveted properties such as anti-inflammatory, immunomodulatory, anti-apoptotic, trophic and angiogenic effects. These functions are believed to be mediated by transient paracrine by-stander mechanisms and cell-to-cell contact in response to the local damaged host tissue environment rather than long-term cell engraftment and cell replacement (Caplan and Correa, 2011; Meyerrose et al., 2010; Prockop, 2007; von Bahr et al., 2012). Equally important, MSCs demonstrate pathotropism by means of chemotaxis-induced homing and migration to injured tissues following intravascular administration (Karp and Leng Teo, 2009).

MSCs have been shown to address and modulate many of the detrimental effects associated with acute and chronic damage in the traumatised spinal cord (Teixeira et al., 2013; Uccelli, 2013; Wright et al., 2011). Ameliorating effects include neuron protection from glutamate excitotoxicity (Lu et al., 2011; Uccelli et al., 2012; Voulgari-Kokota et al., 2012), reduction in levels of stress-associated proteins, pro-inflammatory cytokines and reactive oxygen species (Lanza et al., 2009; Zhou et al., 2009), inhibition of neutrophil adhesion, infiltration and respiratory burst (Pati et al., 2011; Prockop and Oh, 2012; Raffaghello et al., 2008), polarisation of classically activated pro-inflammatory M1 into an alternatively activated pro-reparatory (M2) macrophage phenotype (Giunti et al., 2012; Kim and Hematti, 2009; Nakajima et al., 2012; Zhang et al., 2010), secretion of neurotrophic factors (Crigler et al., 2006; Hawryluk et al., 2012; Li et al., 2002; Nakano et al., 2010; Zhou et al., 2009), enhancement of neural stem cell oligodendrogenic fate and remyelinisation (Inoue et al., 2003; Li et al., 2009; Rivera et al., 2006; Steffenhagen et al., 2012), function as axon guiding strands across lesion site (Hofstetter et al., 2002), reduction of cavity formation and reactive astrocyte proliferation and gliosis (Abrams et al., 2009; Voulgari-Kokota et al., 2012), and stimulation of neurite outgrowth over CSPGs, MAG and Nogo-A (Wright et al., 2007). In addition, research suggests that MSCs themselves may transdifferentiate into glial and neuronal-like cells, at least in vitro, although the exact transdifferentiation potential in vivo remains debated (Chen et al., 2006; Krabbe et al., 2005). Taken together, these observations suggest that administration of MSCs may lead to a net beneficial effect in the recovery process following SCI secondary damage.

Objective

A small number of human studies have investigated the use of MSCs in SCI patients. They have mainly focused on safety and feasibility issues and have lacked a proper randomised control group and have been underpowered. By contrast, an increasing number of rodent studies have during the last decade investigated the efficacy of MSCs on locomotor recovery, a relevant clinical outcome which is considered important among SCI patients (Kwon et al., 2012; Simpson et al., 2012).

Meta-analyses of controlled studies increase the power and precision of the estimated intervention effect and therefore yield a more powerful test of the null hypothesis than any of the separate studies (Higgins and Green, 2008). However, to our knowledge, no quantitative data synthesis of a stem cell therapy for SCI exists. We therefore, systematically reviewed and meta-analyzed studies that assessed the efficacy of MSCs versus control (placebo or no treatment) in an established and widely used animal model of traumatic SCI. Our aim was to determine whether MSCs improved locomotor recovery and to use meta-analysis and meta-regression to explore for variations in effect size. Finally, we subjected the studies to an assessment of bias to exclude systematic errors and to an assessment of risks of play of chance to exclude random errors.

Material and methods

Eligibility criteria

Types of studies: Controlled studies assessing the administration of MSCs to rats with traumatic SCI. No language, publication date, or publication status restrictions were imposed.

Types of participants: Laboratory rats of any age, gender or strain exposed to traumatic SCI induced by contusion or compression. Laceration/transection models of SCI were excluded as this model does not represent the typical crush injury mechanism in humans and has limited rostro-caudal secondary damage spread (Beattie and Bresnahan, 2000; Dietz and Curt, 2006).