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Comprehensive narrative review on the analysis of outcomes from cell transplantation clinical trials for discogenic low back pain

Jordy Schol, Daisuke Sakai*

Tokai University School of Medicine, Department of Orthopedic Surgery, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan

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ABSTRACT

Background: Intervertebral disc (IVD) degeneration is one of the primary causes of low back pain (LBP) and despite a prominent prevalence, present treatment options remain inadequate for a large portion of LBP patients. New developments in regenerative therapeutics offer potentially powerful medical tools to modify this pathology, with specific focus on (stem) cell transplantations. Multiple clinical trials have since reported overall beneficial outcomes favoring cell therapy. Nonetheless, the significance of these improvements is often not (clearly) discussed. As such, this narrative review aims to summarize the significance of the reported improvements from human clinical trials on IVD-targeted cell therapy.

Methods: Through a comprehensive narrative review we discuss the improvements in pain, disability, quality of life, and imaging modalities and reported adverse events following cell therapy for discogenic pain.

Results: Most clinical trials were able to report clear and significant improvements in pain and disability outcomes. Imaging and quality of life improvements however were not as clearly reported but did present some enhancements for a select number of patients. Finally, whether cell therapy can outperform placebo treatment remains intangible.

Conclusions: Our review highlights the clinical significance of observed trends in pain and disability improvement. Nevertheless, reporting quality was found unsatisfactory and large-scale randomized controlled studies remain small in number. Future studies and articles should put more emphasis on improvements in imaging modalities and compare outcomes to (placebo) control groups to fully elucidate the efficacy and safety of cellular therapeutics against LBP.

Introduction

Low back pain (LBP) remains one of the primary causes of disability worldwide, precipitating large economic and social costs to societies [1–3]. Low back pain is a multifactorial and complex symptom, that can originate from a variety of pathophysiological conditions. Regardless, intervertebral disc (IVD) degeneration is a well-established source of back pain, and is believed to form a plurality of LBP cases [4]. Disc degeneration involves a loss in integrity and function of the IVD; specifically, the central nucleus pulposus (NP), annulus fibrosis (AF), and endplate regions. This process may emanate or be exacerbated by wear-and-tear and aging of the IVD or as a consequence of traumatic injury that exceeds the disc's internal regenerative ability. Specifically, a decline in viable NP cell numbers and their activity diminishes the capacity of the disc to maintain its specialized matrix composition [5,6], leading to a gradual reduction in proteoglycan density and collagen architecture disorganization. This impacts the overall IVD biomechanical limits. Loss of disc resilience may result in multiple spinal disorders e.g., spinal stenosis, disc herniation, spinal deformities, etc. Moreover, the degenerative IVD now accommodates senescent and catabolic cells, which secrete highly inflammatory and catabolic factors, thereby potentially attracting immunogenic and inflammatory cells into the otherwise immune-privileged IVD [7]. Among the secreted factors are angiogenic and neurogenic stimulants, which in turn, can vascularize and neo-innervate the inner regions of the otherwise largely avascular and non-innervated disc [8,9]. Finally, the inflamed disc might provoke neighboring nerve, vascular, muscle, and tendon structures, thereby promoting pain sensation in the respective tissues.

Contemporary treatments for discogenic back pain remain largely suboptimal, as they fail to target the underlying pathophysiology. Treatment might comprise the prescription of analgesics or physical therapy. Alternatively, in more severe cases, surgery might be indicated, involving the immobilization or total removal of the affected IVD. For disc removal, the disc will be excised and replaced by either an artificial

FDA device/drug status: Not applicable.

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* Corresponding author.
E-mail address: daisakai@is.icc.u-tokai.ac.jp (D. Sakai).

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disc implant or induced to fuse into a boney segment by bone inducing components. Both arthroplasty and spine fusion are becoming more prevalent, despite controversy surrounding their efficacy [10,11]. Taken together, these conservative and surgical interventions forming the current medical "tool box" for the practitioner remain suboptimal and a treatment strategy between conservative treatment and surgical intervention is bitterly lacking [12].

Evidently, a large unmet medical and socioeconomic need exists for effective therapies able to alleviate discogenic back and neck pain. Upcoming regenerative therapies e.g., gene therapy [13], growth factor injection [14], tissue engineering [15], hold great promise as they aim to target the degeneration cascade underlining the discogenic pain. In particular, cell transplantation has gained significant momentum in the field [12], with multiple clinical trials being reported in recent years. However, the field is progressing rapidly, with increasing numbers of clinical trials being published [12,16]. Moreover, the full potential of cell therapy against LBP remains ambiguous, and recent literature reviews focusses predominantly on qualitative outcomes of the clinical trial. This narrative review discusses the finding of 41 individual reports of 31 separate clinical trials and case reports, aims to assess the impact of cell transplantation through summarizing the rate of score improvements reported in order to determine the alleviation of pain and disability and improving quality of life (QoL) outcomes, so as to determine whether investigatory cell transplantation products are able to demonstrate beneficial effects for LBP patients. Similarly, imaging modality outcomes will be examined to review the ability of transplanted cells to promote the repair of disc anatomy and hydration as a potential regenerative therapeutic. Finally, a careful review of reported serious adverse events (SAE) and adverse events (AE) will be used to grasp the overall safety profile of these cellular products.

Cell therapy

Cellular therapy against discogenic pain involves the transplantation of *de novo* cells in order to (i) replenish or replace (damaged) endemic cells, (ii) activate or alter the (damaged) endemic cell's behavior, and/or (iii) recruit endemic cells into the site of concern [17]. In general, cellular therapy is well-established in the form of bone marrow transplantation for leukemia patients [18], however, its employment for other pathologies and applications has only recently evolved into clinically approved products [19]. Cell therapy for the IVD has first been reported in 1994 [16] and has since been shown incredibly effective as a regenerative product in multiple animal studies [20–23]. As presented in the excellent review of Williams et al. [16] different cells types have been shown to possess the capacity to limit, halt, or even reverse IVD degeneration in multiple disc degeneration models, including reports of histological improvements, improvement in imaging modalities, and inflammation inhibition. However, questions remain regarding the translatability of these animal observations to a human disc environment. Particularly, as human discs are maintained by different cell types, and involve different disc dimensions and biomechanical limits [5,24–27].

Nevertheless, in the past decade, initial pilot studies and phase I/II trials have been completed and reported. Since, multiple reviews on in-human cell therapy for IVD repair and discogenic pain have been reported [17,28–33], nonetheless, they often qualitatively describe the impact of the cell transplantation products on pain, disability, or imaging outcomes, but fail to give a clear, quantitative, and fair impression on the concrete impact of these claimed improvements. Ideally, through meta-analysis the impact of cell therapy is explored and such reports have been published [34,35]. Nonetheless, these reviews are severely limited by the still small number of controlled studies that can be included for analysis, and subsequently small patient cohorts and heterogenous study designs regarding outcome parameters and patient indications.

For this narrative review, we examine multiple reports and studies including case reports, case series, pilot studies, and clinical trials [36–76] (Table 1). Note that in our review, reports discussing the same clinical trial (e.g., reports with multiple follow-up periods) are reported as a single study, referred to by the first-author of the most recent publication. The identified treatments involved predominantly intradiscal transplantation, as well as one case series of intravenous (IV) cell administration [47]. The cell transplantation was employed as a treatment strategy to directly alleviate discogenic pain, to improve outcomes (or limit the deterioration of the IVD) following microdiscectomy, or could be employed to prevent discogenic pain and/or degeneration as a risk from adjacent disc disease. For each identified study we aimed to report outcomes as a change from baseline (both in absolute and as a percentage) and indicate whether these differences were statistically significant. Moreover, where a controlled group was included, a comparison statement has been included.

Pain alleviation

The primary reason LBP patients present themselves to their practitioner is mostly for the pain associated with LBP, as such the prime outcome to be assessed focuses on the alleviation of pain outcomes. These are commonly measured through visual analog scores (VAS; in cm or mm) or numerical rating scale (NRS), thereby providing the patients subjective interpretation of their perceived pain levels. From our review, it is evident that the intervention of cell transplantation is able to alleviate pain in all published cases. Only the work of Haufe and Mork [76], which presents the first identified IVD-based cell therapy trial, examining the transplantation of hematopoietic stem cells (HSC), failed to report any pain improvement in any of their 10 treated cases 1-year post-transplantation. Other studies employing mesenchymal stromal cells (MSC), chondrogenic cells, or mixed cell population were able to present an alleviation of pain scores compared to baseline ranging from 28% [36] to 88% [64] (Table 2).

Supplementation of microdiscectomy surgery

Interestingly, both minimum and maximum pain improvements came from studies that supplemented discectomy procedures with cell transplantation. The 28% was observed in the work of Yoshikawa et al., which examined the impact of transplanting bone marrow derived MSC following disc fenestration of two cases followed for 2 years, while the 88% pain alleviation (=6.3 cm VAS) was reported by Xuan et al. [64] who transplanted autologous IVD-derived cells from the microdissected tissue in 18 cases followed for up to 6 years. Moreover, Xuan et al. [64] were able to compare the effect of their cell therapy to a group subjected to microdiscectomy only, which reported a significant improvement in pain for the cell-treated cohort. It should however be noted that this significant improvement at the 6-year follow-up involved a difference of about 1 cm VAS compared to the control group, suggesting that the main source of pain improvement is likely resulting from the microdiscectomy itself. A similar study by Meisel et al. treating microdiscectomy patients with autologous IVD derived-cells, was similarly able to report alleviation in pain (a 42% reduction), which resulted only in a slight trend of enhanced pain outcomes compared to a discectomy-only cohort. Also, Xu et al. [74] reported enhanced pain outcomes for the cell-treated cohort following microdiscectomy, however, VAS scores were only about 1 cm lower than microdiscectomy-only cohorts. These data do suggest that cell therapy can enhance the pain-outcomes following microdiscectomy, although the clinical impact appears to be minimal.

Cell therapy directed against discogenic pain

Patients treated through cell transplantation as a direct therapeutic for their discogenic pain show overall clearer benefits in pain alleviation. Here the reduction ranges from 31% [66] to 85% [37] pain reduction compared to baseline levels, which represents a VAS reduction

Table 1
General overview of included clinical studies and human case reports examining the effect of cell transplantation for low back pain alleviation or disc degeneration repair.

Author	Year	Ref	FU (y)	Site	Mode	Product	Cell density	Volume and carrier	*n*	Control(s)	*n*	Efficacy	Safety	Type
Yoshikawa	2010	[36]	2	ID	Autologous	BM-MSC	*Unclear*	0.54mL collagen sponge	2	-	-	✔	✔	Mesenchymal stromal cells
Orozco	2011	[37]	1	ID	Autologous	BM-MSC	10×10^6/mL	0.5-1.5mL saline	10	-	-	✔	✔	
Centeno	2017	[38,39]	6	ID*	Autologous	BM-MSC	23×10^6/disc	1-3mL 10-20% PL/PBS	33	-	-	✔	✔	
Noriega	2021	[40–42]	3.5	ID	Allogenic	BM-MSC	12.5×10^6/mL	2mL saline	*Unclear*	Muscle anesthetic	*Unclear*	✔	✔	
Papadimitriou	2021	[43,44]	2	ID	Autologous	BM-MSC	1×10^6/mL	1mL 20% serum/F12	10	-	-	✔	✔	
Amirdelfan	2021	[45,46]	3	ID	Allogenic	MPC	High: 18×10^6/disc Low: 6×10^6/disc	2mL HA	60	HA (Vehicle) Saline (Placebo)	20 20	✔	✔	
Jung	2013	[47]	<0.5	IV	Autologous	AD-MSC	*Unspecified*	*Unspecified*	3	-	-	✘	✔	
Piccirilli	2017	[48]	1	ID	Autologous	AD-MSC	*Unspecified*	1mL solution	2	-	-	✘	✔	
Kumar	2017	[49]	1	ID	Autologous	AD-MSC	High: 20×10^6/disc Low: 10×10^6/disc	2mL HA	5 5	-	-	✔	✔	
Bates	2022	[50]	1	ID	Autologous	AD-MSC	10×10^6/disc	1mL saline	9	-	-	✔	✔	
Zhang	2022	[51]	2	ID	Autologous	AD-MSC	High: 20×10^6/disc Mid: 10×10^6/disc Low: 5×10^6/disc	2mL HA	25 25 25	Saline (Placebo)	25	✘	✘	
Pang	2014	[52]	2	ID	Allogenic	UC-MSC	10×10^6/mL	1mL solution	2	-	-	✔	✔	
Meisel	2006	[53–55]	2	ID	Autologous	IVD-C	*Unspecified*	*Unspecified*	12	Discectomy-only	16	✔	✘	Chondrogenic cells
Mochida	2015	[56]	3	ID	Autologous	NPC	$\sim1.5\times10^6$	0.7 mL saline	9	-	-	✔	✔	
Tschugg	2017	[57,58]	<0.5	ID	Autologous	IVD-C	*Unclear*	PEG + serum + media	12	Discectomy + HA (Vehicle)	12	✘	✔	
Schwan	2017	[59]	*n.a.*	ID	Autologous	IVD-C	*Unspecified*	Saline OR 'polymerizing-scaffold'	10	Discectomy-only	10	✘	✔	
Beall	2020	[60]	1	ID	Allogenic	NPC	*Unclear*	1.75mL NP tissue	16	Saline (Placebo) Conservative care	4 4	✔	✔	
Hunter	2022	[61,62]	1	ID	Allogenic	NPC	*Unclear*	1.75mL NP tissue	140	Saline (Placebo) Conservative care	39 39	✔	✔	
Foley	2022	[63]	1.5	ID	Allogenic	NPC	High: 9×10^6/disc Low: 3×10^6/disc	1mL HA	20 20	Saline (Placebo) HA (Vehicle)	10 10	✔	✔	
Xuan	2022	[64]	6	ID	Autologous	IVD-C	$4\text{-}7\times10^6$/disc	1-3mL saline	18	Discectomy-only	22	✔	✔	
Coric	2013	[65]	1	ID	Allogenic	AC	10×10^6/mL	1-2mL fibrin	15	-	-	✔	✔	
Comella	2017	[66]	1	ID	Autologous	SVF	$30\text{-}60\times10^6$/1-3 disc	1mL PRP	15	-	-	✔	✔	Mixture of cells
Pettine	2017	[67–69]	3	ID	Autologous	BMC	130×10^6/mL	2-3mL solution	26	-	-	✔	✔	
Wolff	2020	[70]	1	ID	Autologous	BMC	*Unspecified*	3mL solution	33	-	-	✔	✔	
Ramos	2020	[71]	1	ID	Autologous	BMC	*Unspecified*	Unspecified mL PRP	1	-	-	✘	✔	
El-Kadiry	2021	[72]	1	ID	Autologous	BMC	*Unspecified*	1-6mL solution	13	-	-	✔	✔	
Jerome	2021	[73]	<0.5	ID	Autologous	BMC	*Unspecified*	*Unspecified*	3	-	-	✘	✔	
Xu	2021	[74]	2	ID	Autologous	BMA	Unspecified	~1.25mL gelatin sponges	15	Discectomy-only Discectomy + AF suture	15 15	✔	✔	
Subach	2011	[75]	1	ID	Autologous	BMA + AT + Plasma	Unspecified	3mL solution	1	-	-	✘	✔	
Haufe	2005	[76]	1	ID	Autologous	HSC	Unspecified	Unspecified	10	-	-	✔	✘	

Efficacy and Safety columns represent whether outcomes are reported presenting overall improvements in pain, disability, quality of life, or image modalities or the presence of (serious) adverse events following cell therapy respectively; ✔: reported, ✘: not reported. * MSC was transplanted intradiscally, treatment was complemented with epidural injection of PL. Abbreviations: AC – Articular cartilage derived cells, AD-MSC- Adipose derived mesenchymal cells, AF – Annulus fibrosis, AT – Adipose tissue, BMA – Bone marrow aspirate, BMC – Bone marrow concentrate, BM-MSC - Bone marrow derived mesenchymal stromal cells, FU – (maximal) Follow up, HA – Hyaluronic acid, HSC – Hematopoietic stem cells, ID – Intradiscal, IV – Intravenous, IVD-C – Intervertebral disc derived cells, MPC - Mesenchymal precursor cells, N.A. – Not applicable, NP – Nucleus pulposus, NPC – Nucleus pulposus cells, PBS – Phosphate buffered saline, PEG - Polyethylene glycol, PL – Platelet lysate, PRP – Platelet rich plasma, REF – Reference, and SVF – Stromal vascular fraction, and UC-MSC – Umbilical cord mesenchymal stromal cells.

Table 2
Overview of improvements in pain outcomes resulting from cell transplantation.

Author	Ref	FU (y)	Improved?	Improvement to baseline at max FU (Percentage change from baseline)	Improvement compared to control groups (Percentage change from baseline)	Type
Yoshikawa	[36]	2	✔	VAS scores improved (=28%)	*n.a.*	Mesenchymal stromal cells
Orozco	[37]	1	✔	Significant 49mm VAS lumbar pain reduction (=71%) Significant 32mm VAS sciatic pain reduction (=85%)	*n.a.*	
Centeno	[38,39]	6	✔	Significant 1.9 NPS reduction (=37%) Average reported SANE-rating was 53	*n.a.*	
Noriega	[40–42]	3.5	✔	Significant reduction in VAS scores	Cell-treated resulted in significant improvement, while control did not, with trend of stronger pain reduction	
	[41]	1	✔	Significant 20mm VAS reduction (=30%)	Trend of slightly enhanced pain reduction (Placebo: 15mm [=24%])	
Papadimitriou	[43,44]	2	✔	2.8 point NRS back pain reduction (=38%) 2.3 point NRS leg pain reduction (=47%)	*n.a.*	
Amirdelfan §	[45,46]	3		Significant 32mm VAS pain reduction low dose (=46%) Significant 42mm VAS pain reduction high dose (=59%) MIC (≥30%): low dose was 53% and high dose was 57% CSC (≥50%): low dose was 43% and high dose was 50%	High dose had significant higher VAS reduction than placebo (=24%), but not carrier group (=42%) High dose significant higher MIC (≥30%) and CSC (≥50%) rates than placebo (20%), but not carrier (45% & 35%)	
Jung	[47]	<0.5	*n.a.*	-	-	
Piccirilli	[48]	1	*n.a.*	-	-	
Kumar	[49]	1	✔	Significant 3.6cm VAS back pain reduction (=55%) 6 pts showed ≥50% VAS improvement	*n.a.*	
Bates	[50]	1	✔	56% of pts reported ≥50% NPRS pain improvement 78% of pts report general NPRS improvement Second injection improved by 40% and worsened for 40% of pts	*n.a.*	
Zhang	[51]	2	*n.a.*	-	-	
Pang	[52]	2	✔	5cm VAS reduction (=66%)	*n.a.*	
Meisel	[53–55]	2	✔	8mm VAS improvement (=42%)† 5 point QBPD improvement (=37%)†	Trend of enhanced outcomes in QBPD and VAS scores compared to discetomy-only group	Chondrogenic cells
Mochida	[56]	3	✔	1.5 JOA-LBPsubscale improvement (=56%)	*n.a.*	
Tschugg	[57,58]	<0.5	?	-	-	
Schwan	[59]	*n.a.*	?	-	-	
Beall	[60]	1	✔	43mm VAS improvement (=78%)	Trend of enhanced VAS improvement compared to placebo control Clear trend of enhanced VAS improvement to conservative treatment before crossover	
Hunter	[61,62]	1	✔	35mm VAS improvement (=54%) 63% of pts reported ≥50% VAS improvement 67% of pts reported ≥20 mm improvement (Crossover: 70% and 91% respectively)	31mm VAS reduction for placebo Trend higher portion of ≥50% VAS and ≥20mm change than placebo (53% and 57% respectively)	
Foley	[63]	1.5	✔	Significant 40mm VAS change for high dose (=59%) compared to MCID Trend of VAS improvement both doses	Trend of enhanced outcomes for high dose group compared to control groups	
Xuan	[64]	6	✔	Significant 6.3cm VAS improvement (=88%)	Significant enhanced improvement compared to discetomy-only cohort	
Coric	[65]	1	✔	Significant 2.6 point NRS improvement (=46%)	*n.a.*	
Comella	[66]	0.5	✔	Significant 2.0cm VAS improvement (=36%) Significant 0.8 PPI improvement (=31%) Slight trend improvement in Dallas Pain Questionnaire	*n.a.*	Mixture of cells
Pettine	[68,69]	3‡	✔	Significant 60mm VAS decrease (=73%)	*n.a.*	
	[67]	1	✔	Significant 46mm VAS improvement (=58%)	*n.a.*	
Wolff	[70]	1	✔	39% of pts reported ≥50% NRS improvement	*n.a.*	
Ramos	[71]	1	*n.a.*	-	-	
El-Kadiry	[72]	1	✔	Significant 3.8cm VAS improvement (=63%) 17.2 BPI improvement (=35%)	*n.a.*	
Jerome	[73]	<0.5	*n.a.*	-	-	
Xu	[74]	2	✔	Significant 5.9cm VAS reduction(=80%)	Significant higher reduction in VAS than discectomy-only or discetomy with AF-suture	
Subach	[75]	1	n.a.	-	-	
Haufe	[76]	1	✘	No pain improvement was observed	*n.a.*	

✔: improvement reported, ✘: no improvement reported, **?**: unreported or unclear results, * Cells were transplanted intradiscally, but complemented with platelet lysate injection at other sites, † Change is observed after microdiscectomy, ‡ Only includes 20/26 patients that did not progress to surgery, § values based on PTI corrected data. **Abbreviations**: AF – Annulus fibrosis, BPI – Back pain index, CSC – Clinically significant change, FU – (maximal) Follow up, JOA – Japanese Orthopedic Association, LBP – Low back pain, MCID – Minimally clinical important differences, MIC – Minimally important change, N.A. – Not applicable, NPS – Numeric pain scale, NPRS - Numeric pain rating scale, NRS – Numerical rating scale, PPI – Present pain index, pts – patients, QBPD - Quebec Back-Pain Disability Scale, REF – Reference, and VAS – Visual analog scale.

of 32mm [37] to 60mm [69], although most commonly improvement rates are reported between 40-50% (Table 2). The reports that included statistical analysis always resulted in a significant pain improvement compared to baseline values. These overall reductions are hopeful and clinically impactful. Additionally, reports determining a responder rate, by employing a threshold of ≥50% VAS improvement, generally report that approximately 40-60% of cases are considered effective responders [49,50,61,70] (Table 2).

Efficacy compared to control groups

Notwithstanding, care should be taken, as current data does suggest a distinct placebo effect, as noted from the 5 placebo-controlled studies included in this review; i.e., Noriega et al. [41,42], the Mesoblast study by Amirdelfan et al. [45,46], the VIVEX Biologics study by Beall et al. [60], Hunter et al. [61,62], and the most recent DiscGenics™ report by Foley et al. [63]. Firstly, 4 out of 5 controlled studies were able to report clear improvements for their placebo and vehicle control cohorts. For example, the report by Beall et al. [61] showed that 53% of saline-treated patients (n=30) were able to report a ≥50% VAS reduction, compared to 63% and 70% of their cell-treated (n=120) and crossover cohort (n=23). Although all 5 controlled trials were able to report a trend of enhanced pain reduction compared to their control groups, only Amirdelfan et al. [45] reported a significant improvement in pain scores and responder rates. Although this was only observed for their high-dose treated cohort and not in comparison with their vehicle-cohort. Notably, however, this significant difference did results in 26 mm additional change in VAS reduction, thereby resulting in a corrected final (3 years follow-up) VAS score of 52mm for the placebo group compared to 28mm for the treated cohort: thus, almost halving the perceived pain for the cell-treated patient. Similarly, Foley et al. [63] reported a trend of enhanced pain reduction of ~10% and ~20% for their placebo- and vehicle cohorts respectively. Moreover, the two crossover studies by Beall et al. [60,61] highlight the potential of general intradiscal injection in pain alleviation as the conservative treatment cohort presented with initial worsening in symptoms that fully inverted to improvement rates similar to cell- and placebo level upon the crossover to cell transplantation. Overall, these studies highlight that cell transplantation can engender a significant and clinically impactful effect on pain alleviation. However, whether these effects can outcompete or are in part a result of the placebo effect requires urgent further examination.

Disability improvements

Supplementation of microdiscectomy surgery

Other than pain outcomes most reports also record improvements in patients' disability index, most commonly measured through the patient-reported Oswestry disability index (ODI) [77] (Table 3). Overall, the disability observations match the trends seen in pain outcomes. A range of 18 [37] to 39 [52] ODI improvements to baseline were recorded, which comes down to a relative reduction of 45% [44] to 76% [52] of baseline ODI scores. Again, focusing on the cell treatment complementing microdiscectomy, a clear trend of improvement in outcomes can be observed. Here, the reports highlight a clear trend or significant improvement in disability outcomes, including significant improvements compared to discectomy-only cohorts in the Xuan et al. [64] and Xu et al. [74] reports. Despite statistical significance, the differences in ODI outcomes for the cell-treated and microdiscectomy-only cohorts appear minimal; e.g., Xu et al. [74] only observed a difference of <10% ODI, and only about 2 points difference from the Japanese Orthopaedic Association (JOA) scores in Xuan et al. [64] Anew questioning the real-life impacts of such improvement.

Cell therapy directed against discogenic pain

Direct cell therapy strategies present a clear improvement in ODI scores, generally resulting in a relative 50-70% ODI improvement compared to baseline, which comes down to approximately 30-point ODI reduction.

Efficacy compared to control groups

However, similarly to the pain outcomes, the controlled clinical trial highlights a strong placebo effect. Namely, control groups are similarly able to result in some improvements in ODI or other disability outcomes, though they are slightly more evident than the pain scores. For instance, Foley et al. [63] reported a significant 31% ODI reduction for their high-dose treated group, while the placebo control presented an approximate reduction of 18% ODI. Notably, a higher variability in perceived ODI improvements was observed in the control group. Sadly, the authors did not yet report on statistical differences between the cell-treated and control cohort outcomes. The controlled study by Amirdelfan et al. [45] similarly presented clearly enhanced outcomes for their cell-treated cohort, resulting in significantly enhanced ODI changes for both low (18 ODI) and high-dose (26 ODI) treated cohorts compared to the placebo group resulting in only 8 ODI reduction, and a significant improvement of the high dose cohort compared to the vehicle group (14 ODI reduction). Also, Beall et al. reported a significantly enhanced responder rate, as indicated by a higher rate of ≥15% ODI improvement, for the cell-treated cohort, although the absolute average difference in ODI at 1-year follow-up is only about 5 points compared to the control group. Finally, Noriega et al. [42] similarly showed clear differences between their control and cell-treated cohorts, resulting in a significant improvement of about 20-point ODI 3.5 years following cell therapy, while the control group showed a trend of about 10-point ODI worsening. Regrettably, no statistical analysis was employed between the two cohorts. Nonetheless, these cumulative observations suggest that cell transplantation can enhance disability outcomes, although an impact of a placebo effect could still be observed, clearer statical and clinically significant differences were observed. Prospective trials should carefully employ examination of their cell product to an appropriate placebo control cohort, to fully elucidate the impact of the injected cells on disability outcomes

Radiological improvements

Cell therapy directed against discogenic pain

Thus far cell therapy has been suggested to be able to alleviate pain and disability outcomes, which form the primary reasons for LBP patients to seek out treatment. Nonetheless, one of the main beneficial effects hypothesized to underly cell transplantation and consequential pain and disability alleviation is the ability to restore (or limit deterioration of) the IVD anatomy. As such, most, studies include magnetic resonance imaging (MRI) or other imaging outcomes to assess the increase in proteoglycan deposition or general IVD degeneration status (Table 4). Unlike the pain and disability outcomes, assessment of radiographic outcomes shows less prominent benefits. From our review, it is clear that at minimum cell transplantation does not seem to negatively impact the IVD, and even suggests the ability to limit the deterioration of the otherwise degenerating IVD. Namely, except for a single increase in Modic change classification reported by Schwan et al. [59] and two times one patient with Pfirrmann grade increase reported by El-Kadiry et al. [72] and Coric et al. [65], all studies reported at least general maintenance of IVD hydration and Pfirrmann classifications during their follow-up (Excluding studies involving microdiscectomy).

Moreover, most studies were able to report some, generally sporadic, improvements in MRI observations. These observations include general trends of reduction in disc bulge sizes as reported by Centeno et al. [38,39]. Bates et al. [50], and Xu et al. [74], suppression

Table 3
Overview of improvements in disability outcomes resulting from cell transplantation.

Author	Ref	FU (y)	Improved?	Improvement to baseline at max FU (Percentage change from baseline)	Improvement compared to control groups (Percentage change from baseline)	Type
Yoshikawa	[36]	2	✔	15 point JOA improvement (=580%)	*n.a.*	Mesenchymal stromal cells
Orozco	[37]	1	✔	Significant 18 ODI reduction (=70%)	*n.a.*	
Centeno	[38,39]	6	✔	31 point FRI reduction (=51%)	*n.a.*	
Noriega	[40–42]	3.5	✔	Significant reduction in ODI	Trend of enhanced ODI outcomes, while placebo group showed trend of worsening ODI.	
	[41]	1	✔	Significant 12 ODI improvement (=35%)	Trend of slightly enhanced ODI reduction than Placebo that showed enhanced 10 ODI (=-42%)	
Papadimitriou	[43,44]	2	✔	18 reduction in ODI (=45%)	*n.a.*	
Amirdelfan[§]	[45,46]	3	✔	Significant 18 ODI reduction for low dose (=35%) Significant 26 ODI reduction for high dose (=51%) MIC (≥30%): low dose was 53% and high dose was 53% CSC (≥50%): low dose was 47% and high dose was 50%	Both doses had significant higher ODI change than placebo (=17%), and high-dose had significant higher ODI change than carrier group (=30%) Both doses significant higher MIC (≥30%) and CSC (≥50%) than placebo (20% & 15%), but not carrier (35% & 25%)	
Jung	[47]	<0.5	*n.a.*	-	-	
Piccirilli	[48]	1	**?**	-	*n.a.*	
Kumar	[49]	1	✔	Significant 26 ODI reduction (=61%) 6 pts showed ≥50% ODI improvement	*n.a.*	
Bates	[50]	1	✔	On average 39% ODI improvement 67% of pts reported ≥30% ODI improvement	*n.a.*	
Zhang	[51]	2	*n.a.*	-	-	
Pang	[52]	2	✔	39 ODI reduction (=76%)	*n.a.*	
Meisel	[53–55]	2	✔	2 point increase in OPDQ (=25%)[†] 4.1% improvement in disability index (=25%)[†]	Trend of enhanced OPDQ and disability index outcomes compared to discetomy-only	Chondrogenic cells
Mochida	[56]	3	✔	13 JOA score improvement (=48%)	*n.a.*	
Tschugg	[57,58]	<0.5	**?**	-	-	
Schwan	[59]	*n.a.*	**?**	-	-	
Beall	[60]	1	✔	38 ODI improvmenet (=71%) Crossover also resulted in clear ODI improvement	No clear enhancement compared to placebo control Clear trend of enhanced ODI improvement to conservative treatment before crossover	
Hunter	[61,62]	1	✔	27 ODI reduction (=53%) 77% of pts reported ≥15 ODI and 85% ≥10 ODI improvement (Crossover: 79% and 79%)	No clear difference in ODI change (Placebo: 24 ODI) Portion of ≥15 and ≥10 ODI improvement was significant than the placebo cohort (57% and 63% respectively)	
Foley	[63]	1.5	✔	Significant 31 ODI improvement for high dose group compared to MCID Trend ODI improvement for both dose group	Trend of enhanced ODI outcomes for high dose group compared to control groups	
Xuan	[64]	6	✔	Significant 14.8 JOA score improvement (=130%)	Significant higher improvement in JOA scores compared to disectomy-only cohort	
Coric	[65]	1	✔	Significant 33 ODI improvement (=62%) 93% of pts reported ≥30% ODI improvement	*n.a.*	
Comella	[66]	0.5		Trend of improved ODI and BDI	*n.a.*	Mixture of cells
Pettine	[68,69]	3[‡]	✔	Significant 57 ODI improvement (=69%)	*n.a.*	
	[67]	1	✔	Significant 32 ODI improvement (=56%)	*n.a.*	
Wolff	[70]	1	✔	31% of pts reported ≥50% ODI improvement	*n.a.*	
Ramos	[71]	1	*n.a.*	-	-	
El-Kadiry	[72]	1	**?**	-	*n.a.*	
Jerome	[73]	<0.5	*n.a.*	-	-	
Xu	[74]	2	✔	Significant 41.5 ODI reduction (=66%)	Significant higher reduction in ODI than discectomy-only or discetomy with AF-suture	
Subach	[75]	1	n.a.	-	-	
Haufe	[76]	1	?	Unspecified	*n.a.*	

✔: improvement reported, ✘: no improvement reported, **?**: unreported or unclear results, * Cells were transplanted intradiscally, but complemented with platelet lysate injection at other sites, † Change is observed after microdiscectomy, ‡ Only includes 20/26 patients that did not progress to surgery, § values based on PTI corrected data. Abbreviations: AF: Annulus fibrosis, FRI – Functional rating index, FU – (maximal) follow-up, JOA – Japanese Orthopedic Association, MCID – Minimally clinical important differences, N.A. – Not applicable, ODI – Oswestry disability index, OPDQ - Oswestry low back pain disability questionnaire, and REF – Reference.

of high-intensity zones (in 89% of patients as reported by Coric et al. [65]), vacuum phenomenon alleviation[36], and AF fissure improvements [50]. Moreover, many studies were able to report improvement in Pfirrmann classifications, although the number of patients presenting with this regenerative outcome involved only a fraction of the entire cohort (Table 4). The largest proportion was reported by Pettine et al., who were able to report a Pfirrmann grade improvement in 40% of their treated cohort. Notably, however, is the large placebo-controlled study of Amirdelfan et al. [45] which were unable to show any significant difference in Pfirrmann improvement rates between cell-treated and con-

Table 4
Overview of improvements in imaging modality outcomes resulting from cell transplantation.

Author	Ref	FU (y)	Improved?	Improvement to baseline at max FU (Percentage change from baseline)	Improvement compared to control groups (Percentage change from baseline)	Type
Yoshikawa	[36]	2	✔	Improvement in T2 intensity Improvement in vacuum phenomenon	*n.a.*	Mesenchymal stromal cells
Orozco	[37]	1	•	No deterioration in disc height No change in disc hydration	*n.a.*	
Centeno	[38,39]	6	✔	17/20 pts (85%) displayed decrease in disc bulge size	*n.a.*	
Noriega	[40–42]	3.5	✔	Significant improvement of 0.65 Pfirrmann grades	Significant worsening of 1.01 Pfirmann grades in control Trend of enhanced Pfirrmann results	
Papadimitriou	[43,44]	2	•	No deterioration of IVD	*n.a.*	
Amirdelfan	[45,46]	3	•	1 modified Pfirrman grade improvement for low dose 1 modified Pfirrman grade improvement for high dose	No differences in rates of modified Pfirrmann grades between cohorts	
Jung	[47]	<0.5	*n.a.*	-	-	
Piccirilli	[48]	1	?	-	*n.a.*	
Kumar	[49]	1	✔	No decrease in disc height observered 1 pts showed Pfirrmann grade improvement No deterioration in Pfirrmann grades was observed ADC values increased by 47.2 (=4%)	*n.a.*	
Bates	[50]	1	✔	No worsening reported in MRI findings 3 patients showed AF fissures improvement 2 patients showed reduction in disc bulge/protrusion	*n.a.*	
Zhang	[51]	2	*n.a.*	-	-	
Pang	[52]	2	✔	1 pts reported increase in T2-intensity	*n.a.*	
Meisel	[53–55]	2	✔	2.8 mm increasse in disc height (=13%)† Trend of increase in proportion of "normal" disc water content of treated and neighboring discs†	Trend of doubling in disc height increase compared to disectomy-only group Trend of higher "normal" water content proportion in treated and neighboring discs compared to discectomy-only group	Chondrogenic cells
Mochida	[56]	3	✔	1 pts reported improvement in Pfirrmann grade No deterioration in discs reported	*n.a.*	
Tschugg	[57,58]	<0.5	?	-	-	
Schwan	[59]	*n.a.*	✘	1 pts presented Modic I change	-	
Beall	[60]	1	✔	Anatomic improvement on MRI was observed	-	
Hunter	[61,62]	1	?	-	-	
Foley	[63]	1.5	✔	Improvement in disc volume for high dose cohort (Significant improvement at 52w observation)	Controls showed worsening of disc volume Trend of enhanced outcomes both doses	
Xuan	[64]	6	✔	Significant 5.3% DHI reduction (=14%)* Significant 6.3% hydration reduction (=20%)*	Significant lower DHI reduction compared to discectomy-only cohort Significant lower hydration reduction compared to disectomy only cohort	
Coric	[65]	1	✔	10/13 pts (77%) showed MRI improvements 1/13 pts (8%) showed MRI based deterioration 8/9 pts showed improvement of HIZ	*n.a.*	
Comella	[66]	0.5	?	-	*n.a.*	Mixture of cells
Pettine	[68,69]	3***	?	-	*n.a.*	
	[67]	1	✔	8/20 (=40%) of patients presented Pfirrmann grade improvement	*n.a.*	
Wolff	[70]	1	?	-	*n.a.*	
Ramos	[71]	1	*n.a.*	-	-	
El-Kadiry	[72]	1	✔	Significant 0.8 mm increase in DHI (=11%) 4 discs improved in Pfirrmann grading 1 disc worsened in Pfirrmann grading	*n.a.*	
Jerome	[73]	<0.5	*n.a.*	-	-	
Xu	[74]	2	✔	Significant 17.2% DHI reduction* No deterioration in Pfirrmann grading*	Significant lower DHI reduction than other groups Other groups showed significant worsening in Pfirrmann gradings Cell-treated cohorts showed significant higher reduction in disc protrusion size	
Subach	[75]	1	n.a.	-	-	
Haufe	[76]	1	?	-	*n.a.*	

✔: improvement reported, •; no clear improvement reported ✘: worsening reported, **?**: unreported or unclear results, * Any reduction is likely resulting from the discectomy procedure that is complemented with cell transplantation. † Change following discectomy. Abbreviations: ADC – Apparent diffusion coefficient, AF – Annulus fibrosis, DHI - Disc height index, FU – (maximal) follow-up, HIZ – High-intensity zone, N.A. – Not applicable, and MRI: Magnetic resonance imaging.

trol cohorts. On the contrary, Noriega et al. [40–42] was able to report a significant improvement in Pfirrmann classification for their cell-treated cohort, while their control cohort presented a significant worsening in Pfirrmann grades. Sadly, no statistical comparison was made between the two groups. It should however be noted, that an increase in a single Pfirrmann classification grade, might resemble a relatively demanding degree of regeneration [78]. As such, MRI-derived disc hydration values, e.g., T2 or apparent diffusion coefficient (ADC) intensity values, might be more sensitive and can present a more gradual impression of disc improvement. Unfortunately, the number of studies examining and/or reporting such parameters is limited. Of the studies that reported MRI-based intensity outcomes, minimal improvements were reported. Pang et al. [52] reported that 1 of 2 patients showed T2-intensity increases following cell injection, Yoshikawa et al. [36] reported general T2 intensity improvements, and Kumar et al. [49] was able to report an average of 4% increase in ADC values compared to baseline.

Supplementation of microdiscectomy surgery

When examining the impact of cell transplantation accompanying microdiscectomy, a potentially clearer impact can be recognized. For example, all controlled studies were able to show a significantly lower reduction in disc height following microdiscectomy compared to the discectomy-only group. Xuan et al. [64] resulted in a difference of an estimated 3%-disc height index (DHI), while Xu et al. [74] present an estimated increase of about 12%. Similarly, Meisel et al. [53–55] were able to report a trend of maintaining about double the DHI compared to the control group. Also, Xu et al. reported significant worsening in Pfirrmann grades for the control groups, while the cell-treated group was largely able to maintain their Pfirrmann classification. Xuan et al. also were able to present a significantly lower rate of disc hydration loss compared to the discectomy-only group, which resulted in more than 0.15 normalized ADC retention. However, whether any of these improvements result in enhanced clinical outcomes for the patient or reduces the risk of future spinal events remains to be fully elucidated.

Altogether, these observations show that cell transplantation is likely able to some extent to halt the progression of disc degeneration and does have the potential to regenerate the discs, although these observations still remain rare and limited. Future efforts should aim to employ more sensitive and long-term observations to fully grasp the regenerative potential of these cell transplantation products.

Quality of life assessments

QoL assessments are patient-based outcome measures that can give an impression of the effect of LBP and treatment on the happiness and satisfaction of the patient. These outcomes are valuable tools to assess the impact of cell therapy on a broader and corporal domain of the patient and its potential socioeconomic influence. Yet, the number of studies (clearly) reporting on such outcomes remains limited. An overview of outcomes is included in supplementary table 1. The most commonly employed questionnaires are either Short Form (SF)-12 or SF-36, which in turn are generally separated in their physical and mental subcomponents [79]. For the studies that did report on QoL outcomes, a general trend of improvement in outcomes was reported. However, the rate of improvement varied greatly among the different studies. A repeating observation, however, was that the cell-treated groups were generally able to present a clear and significant improvement in SF-12/36 physical subscale outcomes, while the mental component presented less evident improvements. For the controlled studies, Amirdelfan et al. [45] were able to report significantly enhanced SF-36 outcomes for the high-dose group compared to both placebo- and vehicle-control cohorts. Similarly, Foley et al. [63] reported a trend of enhanced EuroQol 5-dimensions (EQ-5D) questionnaire scores for their high-dose cohort. Comparing cell treatment complimenting discectomy revealed significantly enhanced SF-36 outcomes compared to the discectomy-only cohort by Xuan et al. [64], while Xu et al. [74] was unable to present clear differences.

Safety assessment

General adverse events

In addition to effectiveness, the safety of cell therapy and cell therapy products is of critical importance. Moreover, the studies currently included are case-report, case series, pilot studies, and phase I/II studies and as such, their predominant role is to assess the safety profile and applicability of the cell-based treatments. Of the at least 605 cell-treated patients recognized; 216 were treated by MSC, 272 with chondrogenic cells, and 107 were treated with a mixture of unspecific cell populations (Table 1). From these reports, a total of at least 174 separate AE were reported (Table 5). Markedly, not all recorded AE are likely to be treatment-related; e.g., the ischemic heart attack and myocardial infarction reported by Hunter et al. [62] were not considered an effect of the treatment. Of the 174 AE, 9 AE were identified as SAE by the authors; which included pulmonary embolism, bacteremia, osteomyelitis, discitis, lumbar disc herniation, cauda equina syndrome, etc. No cases of death were reported. The most common AE appears to be the presentation of pain, which includes back pain, leg pain, or otherwise. Another common AE occurrence appears to be disc (re)herniation or disc protrusion. These two types of AE are not unexpected, as these are inherent to the disc degeneration pathophysiology. It thus remains unclear if these AE result from the treatment or rather the inability of the treatment to resolve the degenerative process.

Infectious adverse events

Another set of AE are infectious in nature, including discitis, spondylodiscitis, osteomyelitis, etc. Infections risks are intrinsic to surgery and moreover the introduction of foreign (cultured) material in the disc is likely to pose additional risks for potential contamination. As such these AE are not unexpected. As highlighted in the excellent review of Jerome et al. [73] multiple strategies could be considered for reducing the risk of introducing pathogenic materials during the cell transplantation procedure. Considerations of antibiotics, surgical technique, and allogenic cell products might be able to limit the occurrence of transfections resulting from intradiscal injection. Moreover, the seemingly most severe cases identified in our review, i.e., presenting severe discal infections, involve two case reports from Ramos et al. [71] and Subach et al. [75], who treated their patients after they received “stem cell” therapies from an outside provider. With those caveats, the overall rate of AE appears low and relatively mild, and the safety impression by all authors was considered good. Specifically, no articles thus far have been reported that suggest severe immunogenic reactions in response to the transplanted cells, severe unexpected deterioration within the treated discs, tumor formation, or undesired tissue formation elsewhere. Furthermore, the work by Garcia-Sancho et al. [40] suggests the overall safety of allogenic cell transplantation, as human leukocyte antigen mismatching did not result in immunogenic reactivity nor diminishment of efficacy. Nonetheless, the rate of AE and SAE requires careful monitoring and will require highly-powered, prospective, and controlled trials to be able to fully grasp the overall safety profile of cell transplantation therapy and the different cell products.

Discussion

General impression of cell therapeutics

From our current review, we believe it is fair to suggest that (i) cell therapy appears to be a relatively safe treatment strategy and (ii) that the cell transplant injection can alleviate pain and disability outcomes.

Table 5
Overview of the (serious) adverse events reported following cell transplantation.

Author	Ref	*n*	SAE	AE	Description	Type
Yoshikawa	[36]	2	?	?	-	Mesenchymal
Orozco	[37]	10	✘	?	-	stromal cells
Centeno	[38,39]	33	✘	√	Unspecified complaints (n=6) Pain (n=3) Large herniated disc (n=1)	
Noriega	[40–42]	*Unclear*	✘	√	Pain (n=11)*	
Papadimitriou	[43,44]	10	✘	✘	-	
Amirdelfan	[45,46]	60	√	√	Pain (n=34) Arthralgia (n=6) Muscle spams (n=6) Elevated CRP (n=2) *Pharyngitis streptococcal* (n=2)	
Jung	[47]	3	√	√	Pulmonary embolism (n=3)	
Piccirilli	[48]	2	✘	✘	-	
Kumar	[49]	10	✘	✘	-	
Bates	[50]	9	✘	√	Pain flare (n=1)	
Zhang	[51]	75	*n.a.*	*n.a.*	-	
Pang	[52]	2	✘	✘	-	
Meisel	[53–55]	12	?	?	-	Chondrogenic
Mochida	[56]	9	✘	✘	-	cells
Tschugg	[57,58]	12	√	√	Unspecified complaints (n=2) IVD protrusion (n=1) Nasal pharyngitis (n=3)	
Schwan	[59]	10	√	√	Recurrent disc herniation (n=10)	
Beall	[60]	16	✘	√	Muscle injury (n=1) RBC sediment rate increase (n=1) Pain (n=9) Burning sensation (n=1)	
Hunter	[61,62]	140	√	√	Unspecified complaints (n=36) Myocardial infarction (n=1) Transient ischemic attack (n=1) Bacteremia (n=1) Osteomyelitis (n=2) Spinal osteoarthritis (n=1) Pneumonia (n=1) Pain (n=4)	
Foley	[63]	40	✘	?	-	
Xuan	[64]	18	√	√	Pain (n=3) Disc reherniation (n=1)	
Coric	[65]	15	✘	✘	-	
Comella	[66]	15	✘	√	Soreness (n=?)	Mixture of
Pettine	[67–69]	26	✘	√	Pain (n=?)	cells
Wolff	[70]	33	✘	✘	-	
Ramos	[71]	1	√	√	Lumbar discitis (n=1) Osteomyelitis (n=1)	
El-Kadiry	[72]	13	✘	✘	-	
Jerome	[73]	3	√	√	Pain (n=3) Constipation (n=2) Fever (n=2) Elevated CRP (n=2) Discitis (n=1) Spondylodiscitis (n=2) Epidural abscess (n=1)	
Xu	[74]	15	✘	✘	-	
Subach	[75]	1	√	√	Disc extrusion (n=1) Osteomyelitis (n=1) Discitis (n=1) Epidural abscess (n=1) Cauda equina (n=1)	
Haufe	[76]	10	?	?	-	

√: AE reported, ✘: no AE reported, **?**: unreported or unclear results. Abbreviations: AE – Adverse event, CRP – C-reactive protein, IVD – Intervertebral disc, N.A. – Not applicable, and SAE – Serious adverse event, RBC – Red blood cell count, and REF – Reference.

Nonetheless, the ability of cells to trump placebo or sham treatment remains contentious. Moreover, whether transplanted cells could regenerate sufficient quantities of the IVD matrix to result in observable and clinically beneficial outcomes similarly requires more careful inspection. In addition, the cost-effectiveness of cell therapy requires prudent examination in the future and should similarly be compared to alternative standard treatment strategies to ensure healthcare spending is allocated at optimum.

From this review, it is evident that the clinical study of cell therapy is still in early stage of development. From the presently reported trials only the work of Amirdelfan et al. [45], Foley et al. [63], Hunter et al. [60–62], and Xu et al. [74] involved clinical trials that included reports of more than 50 patients. Additional large-scale randomized (placebo) controlled clinical trials are needed in order to get a better impression of the potential of cell therapy or to determine optimal treatment strategies and products. Specifically, the results of multiple clinical trials currently

ongoing or recruiting are highly anticipated [28,80], and will hopefully give more insights into the potential of cellular therapeutics for disc degeneration and its related symptoms. We hope that this literature review and findings will help with the design of future clinical trials for cell therapy, by providing resources for patient size calculations as well as parameter and study design considerations.

Cell product optimization

Contemporary cell transplantation products, involve highly complicated production processes within strict regulatory frameworks [81,82] to ensure cell product potency, safety, marketability, and reliability. Despite these aspects, the investigatory cell products themselves are relatively simple in nature, involving generally ill-defined cell populations, typically unoptimized for their function in the harsh disc environment, and are derived from different sources and donors. For example, the majority of reports reviewed here did not include a presentation of the surface markers expression profile of the transplanted cells. Only a small set of reports included marker expression analysis, and generally involved an assessment to confirm an MSC phenotype [83], but did not further select for a distinct cell population expected to be optimally posed to regenerate or survive within the IVD. This could be a critical feature to further enhance the potency of the cellular product; for example the work of Pettine et al. which identified the prognostic role of CD34+ cells within their cell product for beneficial pain outcomes [67–69]. Selection of key cell markers has been suggested to be a promising tool for identifying optimal cell candidates in multiple *in vitro* and animal studies, and could allow the selection of progenitor cell populations, e.g. Tie2 [84–86] for NP progenitor cell selection, or more highly regenerative cell populations, by for example optimizing for CD146 expressing MSC [87,88].

Alternatively, cells could be primed to take on a more well-suited phenotype able to strive and survive within the harsh IVD environment. Such an approach was employed by Centeno et al. [38,39] using hypoxic culture conditions for their MSC and by Mochida et al. [56] using MSC coculture conditions to rejuvenate their isolated NP cells. Future prospects are likely to see further optimizations and augmentations of cells, to create products optimally designed for the IVD environment and therapeutic impacts. Such, tools might include the differentiation of cells from induced pluripotent stem cell sources [89–91] or genetic augmentation of cells e.g., MSCs overexpressing with chondrogenic master regulator SRY-Box Transcription Factor 9 (SOX9) [92]. However, such optimizations would come with additional costs and regulatory requirements and thus would require careful deliberation [81,82,93,94].

Clinical outcome parameters and patient stratification

Another critical aspect to consider is the outcome parameters implemented. Pain, disability, and QoL outcomes remain highly subjective and from the current clinical trial data appear highly impressionable by the placebo effect. More quantitative and objective values would therefore ideally be employed. MRI and other radiographic examinations are therefore promising tools and have shown the potential of cell transplants to improve disc quality (Table 4). Nonetheless, current clinical MRI equipment and sequences are limited in their ability to highlight a clear connection between back pain and disc degeneration, as asymptomatic patients can also present abnormal MRI findings and vice versa [95–97]. As such more sophisticated and sensitive MRI sequences are highly anticipated. Also, upcoming techniques, such as functional MRI, could potentially give more insight into pain and thus provide more objective outcomes than survey-based results. Moreover, from the current clinical studies it has been suggested that a selection of treated patients emerge as responders (e.g., Noriega et al. [40–42] and Amirdelfan et al. [45]). Hence, potential selection and stratification of these patients would likely be critical for the successful effective implementation of cell therapeutics. Nevertheless, it remains unclear which specific features are predictive for effective treatment. Here, advances in MRI technology are also expected to play a pivotal role [95].

Techniques to better visualize the full integrity of the AF, permeability of the endplate, source of back pain, and biomechanical composition of the IVD could prove beneficial as inclusion or exclusion criteria. Particularly, due to the largely avascular nature of the IVD and thereby limited nutrient and gas availability in the disc[8]. These aspect can be further worsened by endplate calcification [98,99] and in silico models have emphasized the potential impact of progression of degeneration on the access to sufficient resources for transplanted cells to prosper [99,100]. A suggested limitation might be the need for early transplantation of cells to be effective, and a set of trials have suggested higher efficacy rates among younger patients (e.g., see Pettine et al. [67] and Hunter et al. [62]). Again, emphasizing the likely need to stratify optimal patient candidates. The previous also underlines the likely misguided focus of cell therapy solely on the NP. Additional strategies for AF and endplate repair, or combined approaches, will likely be beneficial for specific LBP conditions and warrants further investigation [101]. Similarly, alternative strategies to intradiscal injection that could introduce the beneficial (effects of) cells into the disc can potentially reduce the dependency on the deteriorated IVD integrity [23,102].

Suboptimal reporting standards

Finally, we would like to emphasize the overall poor quality of reporting on in-human cellular therapeutic trials for discogenic pain. As can be seen from our tabular overview, key aspects of the cell product, intervention techniques, and study designs remain unspecified or are unclear in a number of studies. Moreover, various reports choose to not include a clear overview of their outcome measures, whether that be in a table or in graphical format. Similarly, simple statistical analysis defining changes to baseline values or between different groups is not consistently included or remains obscure. As such, we would urge authors reporting on cell therapeutics as well as peer-reviewers and editors to be more stringent on the expected quality and data availability of reports in order in order to advance the potential and quality of cellular therapeutics as a much-awaited treatment option for LBP patients.

Conclusions

Our review highlights the overall safety and potential of cell transplantation to alleviate LBP and associated disability, thereby offering a possibely low-risk and minimally invasive treatment for a large cohort of LBP patients that currently have no treatment options available to them. Moreover, in some cases improvements on imaging modalities can be observed, highlighting the potential for long-term effects. Nonetheless, the potential of cell therapy compared to placebo or vehicle groups is less evident. Although trends of improvement can be observed, the statistical as well as clinical significance remains highly uncertain. An urgent need for large-scale, randomized, (placebo) controlled studies is needed to get an insight to the full potential of cell therapeutics. Moreover, their cost-effectiveness studies should be carefully examined as these types of studies are still severely lacking.

Short summary

Low back pain is the primary cause of disability worldwide and treatment options remain inadequate for a large portion of patients. New developments in regenerative medicine are highly anticipated. In this review, we highlight and discuss the quantitative outcomes of pain, disability, quality of life, and imaging modalities following cell transplantation for low back pain, highlighting the overall beneficial impacts of cell therapy, although its effectiveness in comparison to placebo controls remains unresolved.

Declarations of Competing Interest

Daisuke Sakai is a paid scientific advisor for TUNZ Pharma Inc. (Osaka, Japan)

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.xnsj.2022.100195.

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