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REVIEW

Cell therapy for intervertebral disc herniation and degenerative disc disease: clinical trials

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Abstract

Low back pain is the primary cause of disability and is highly associated with progression of intervertebral disc degeneration. Current treatment options are limited and fail to address the origin of the problem. New advancements in cellular therapies might offer novel and potent strategies for low back pain patients. In this review, we summarize and discuss the contemporary status of in-human trials investigating cellular transplantation for treatment of low back pain. We aim to highlight current trends, shortcomings, and hurdles for effective clinical trials and consecutive commercialization.

Keywords Clinical trials · Cell therapy · Regenerative medicine · Intervertebral disc · Degeneration

Introduction

Low back pain (LBP) is recognized as the primary cause of disability worldwide, affecting an estimated 632 million people [1, 2]. The consequential engendered societal burden is severe, with USA socioeconomic costs estimated to exceed an annual $100 billion [3, 4]. Therefore, small reductions in LBP-related healthcare or disability rates could result in significant economic benefits [5]. Although a direct cause of LBP remains elusive, the symptoms associate with the onset and progression of intervertebral disc (IVD) degeneration. IVDs are the fibrocartilage tissue structures between each two vertebrae, absorbing and distributing complex loads along the spine. A nucleus pulposus (NP) core constituted of water and proteoglycans, which is laterally constricted by layers of radially aligned collagen fibers forming the annulus fibrosus (AF), form the IVD. On the IVD interface with the vertebrae, a thin cartilage layer is present; the endplate (EP), which provides the primary source of nourishment exchange, between the well-vascularized vertebrae and the non-vascularized discs. IVD degeneration is considered a complex molecular cascade involving catabolic factors that alter endemic cellular behaviour [6]. Due to aging, trauma, genetics, and lifestyle factors, cells in the NP progressively acquire a senescent phenotype, secrete catabolic factors, and alter ECM deposition, changing the NP from a hydrated tissue to a fibrotic structure [6]. The changes in NP-ECM engender compromised biomechanical features, potentially promoting disorders such as spondylolisthesis, kyphoscoliosis, and canal stenosis.

Most occurrences of LBP are mild and generally managed with conservative interventions, e.g., physical therapy, or administration of analgesics. Considering the large patient population, LBP is the primary reason for non-cancer opioid prescriptions in the USA [7]. Although, conservative treatments are able to alleviate symptoms for some, a subgroup will progress to a chronic LBP state. For patients at severe stages, surgical intervention will be considered, and the degenerated IVD surgery rate has shown tremendous growth in the last decades [8]. For herniated or bulging discs, with signs of compressed spinal nerves, (micro) discectomy will be considered. Alternatively, complete IVD replacement will be attempted, either by fusion surgery or total disc arthroplasty; however, these surgical procedures are highly controversial. Firstly, the nociceptive source can often not be identified and therefore surgical intervention should require caution [9]. Secondly, the efficacy of these treatments is highly debated, despite being invasive and extremely costly [10]. In a randomized controlled clinical study of 222 LBP patients undergoing

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fusion surgery, only 33% of patients reported improvement in pain, compared to 7% in the non-surgical group [11]. In a different retrospective cohort study, return to work rate was demonstrated as 67% for non-treated patients, compared to 26% of fusion-treated patients [12]. Moreover, 27% of the fusion participants required reoperation, and 11% progressed to a permanent disability compared to 2% in the non-surgical group [12]. Finally, these surgeries do not intend to restore the IVD, but instead immobilizes the joint and induces further degeneration in the manipulated and neighboring discs [13]. In short, an urgent unmet demand exists for novel therapies able to prevent, delay, or completely replace the need for the suboptimal and costly surgical interventions (Fig. 1).

Recent focus has been put on the development of novel regenerative therapies aimed at re-establishing a healthy IVD. Such treatments could involve protein, compound, biomaterial injections, and gene therapy, which aim to redirect or support endemic cells [14]. Also, investigators are exploring tissue engineering strategies to create biological IVD replacements [15, 16]. In this review paper, we will focus on cell therapy, a regenerative strategy that in recent years has gained significant momentum, with a variety of clinical trials reported in recent years [17, 18]. Here, we present a comprehensive review on identified publications [10, 19–35] involving in-human cell transplantation as treatment for IVD degeneration, lumbar IVD herniation, or LBP. The aim of the review is to (1) provide a clear oversight of the state-of-the-art for IVD cell therapy, (2) identify the current shortcomings and trends with regard to patient outcomes and study designs, and (3) discuss obstacles for the commercialization of the cell therapy products.

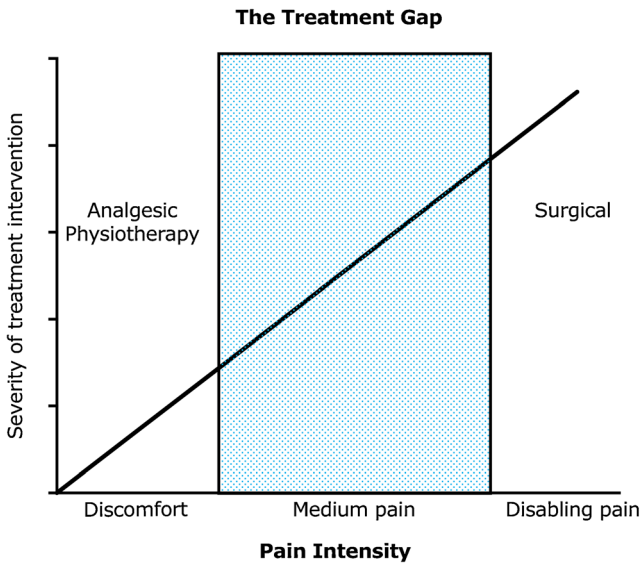

Fig. 1 The therapy gap for intervertebral disc degeneration and herniation A graphical representation of the gap in treatment options for the treatment of IVD degeneration associated low back pain. Graph made by GraphPad Prism (GraphPad Inc., San Diego, California, USA)

Clinical studies: design and outcomes

As of August 2018, we recognized 14 separate in-human clinical studies, spreading over 18 different peer-reviewed publications. [10, 19–35] (Tables 1, 2, 3, and 4). Compared to a recent review [17] from the beginning of 2017, 5 additional studies have been identified [19, 20, 24, 28, 33], suggesting a trend of acceleration in in-human cell therapy trials (Fig. 2). The design of the studies ranges from case-reports to randomized controlled studies, with follow-up periods spanning half a year to six years. The combined 14 in-human studies involve 185 participants, with a range of 2–33 patients per study. Only three trials [26, 28, 33], implemented a control group (Table 1). Meisel et al. [25, 26] applied IVD-derived chondrocytes following discectomy and compared it to a discectomy-only group. Tschugg et al. [33] will compare their IVD-derived chondrocyte transplant encapsulated in a hyaluronic acid-derived product, in comparison to patients receiving identical product without the addition of encapsulated cells. Finally, Noriega et al. [28] applied anaesthetic injected into the paravertebral muscles as a placebo control to assess their mesenchymal stem cell (MSC) product, in a double-blinded randomized controlled study. For all other studies, no control group was included and outcome parameters are presented relative to pre-transplantation status.

The current clinical studies are still within pilot or phase I stage, for which the primary focus is on safety and tolerability characteristics of their products. From all 14 trials, only two reported serious adverse events (SAEs) during their follow-up, both reporting one patient presenting disc herniation after treatment. [19, 33]

Within the included studies, two trials [28, 33, 34] were labeled as a phase I/II study, which would entail investigating the efficacy of the assessed therapy. Tschugg et al. [33] in current publication only reports on the primary early-stage safety findings. Each study did include outcome parameters with regard to initial efficacy assessments. The primary reason for the development of the cellular products is to alleviate pain, to minimize the engendered disability, thereby improving the quality of life. These features should ideally be the primary outcome parameters assessed within the clinical trials [18, 36]. The effect of the treatment should be aimed at long-term results (> 6 months), as conservative interventions are generally able to establish short-term pain alleviation [18, 36]. Secondarily, the cell-based therapies are expected to restore the IVD microenvironment and biomechanical features, and thus ideally, these factors should also be assessed [36]. Twelve out of the 14 clinic trials directly reported changes in pain parameters. One study did not report pain outcomes but will assess these in the future [33, 34], while Elabd et al. [22] do not report pain parameters. Most common approach of assessing pain is by applying visual analog scale (VAS) or numerical rating scale (NRS) pain scores (Tables 2 and 3)

Table 1 Overview published in-human study designs

Author	Ref	Year	Location	Trial ID	Phase	Type	Summarized indication	Participant (n)[a]	Sex	Age (±SD)	Control (n)[a]	Control groups	Duration (year)[b]
Centeno et al.	[19]	2017	USA	NCT03011398	–	*Unspecified*	IVD degeneration, with posterior disc bulge and radicular pain.	33	M (21) F (12)	40 (±14)	*NA*	None	6
Comella et al.	[20]	2017	USA	NCT02097862	–	Open label, non-randomized, multicenter study	Degeneration at one, two or three lumbar discs, with predominant low back pain	15	M (11) F (4)	52	*NA*	None	0.5
Coric et al.	[21]	2013	USA	BB-IND 13985	–	*Unspecified*	Single-level, symptomatic lumbar disc degeneration from L3 to S1, with AF integrity	15	M (9) F (6)	40	*NA*	None	1
Elabd et al.	[22]	2016	USA	–	–	*Unspecified*	Function impairment by low back pain associated with IVD degenerated	5	M (3) F (2)	40 (± 10)	*NA*	None	4–6
Haufe and Mork	[23]	2006	USA	–	–	*Unspecified*	Ineffectively endoscopic discectomy treated LBP patients, considered for IVD fusion intervention	10	M (5) F (5)	*Unspecified*	*NA*	None	1
Kumar et al.	[24]	2017	South Korea	NCT02338271	Phase I	Single-arm, open label, single center, clinical trial	Axial chronic discogenic LBP for at least 3 months	10	M (6) F (4)	44 (± 10)	*NA*	None	1
Meisel et al.	[25] [26]	2006	Germany	–	–	Prospective, randomized, multicenter study	Single-level traumatic lumbar disc herniation OR persistent unspecified symptoms, undergoing discectomy	12	–	*Unspecified*	16	No transplant (discectomy only)	2
Mochida et al.	[27]	2015	Japan	–	Phase I	*Unspecified*	Patients, ranging from 20 to 29 years old, with moderate IVD degeneration	9	M (8) F (1)	26 (± 4)	*NA*	None	3
Noriega et al.	[28]	2017	Spain	EudraCT 2012-004444-30 NCT01860417	Phase I/II	Prospective, randomized, blinded, and controlled study	IVD degeneration of one or two lumbar discs with predominant back pain	24	M (17) F (7)	38	*NA*	Paravertebral musculature anesthetic injection	1
Orozco et al.	[29]	2011	Spain	EudraCT 2008-001191-68	Phase I	*Unspecified*	IVD degeneration of one or two lumbar discs with predominant back pain	10	M (4) F (6)	35 (± 7)	*NA*	None	1
Pang et al.	[30]	2014	China	–	–	*Unspecified*	Painful IVD with confirmed outer AF	2	M (1) F (1)	42 (± 5)	*NA*	None	2

Table 1 (continued)

Author	Ref	Year	Location	Trial ID	Phase	Type	Summarized indication	Participant (n)[a]	Sex	Age (±SD)	Control (n)[a]	Control groups	Duration (year)[b]
							disruption, and neighboring discs appearing healthy						
Pettine et al.	[10] [31] [32]	2014	USA	–	–	Open label, prospective, non-randomized, single-center two-arm pilot study	Centralized chronic low back pain that increased with activity	26	M (11) F (15)	38	*NA*	None	3
Tschugg et al.	[33]	2017	Germany	EudraCT 2010–023830-22	Phase I/II	Non-confirmatory, prospective, multicenter, unmasked, randomized study	Single-level symptomatic lumbar disc herniation that is scheduled for sequestrectomy	12	M (10)	45 (± 7)	8	Only carrier: Albumin, hyaluronic acid gel	5
	[34]		Austria	NTC01640457					F (2)				
Yoshikawa et al.	[35]	2010	Japan	–	–	*Unspecified*	IVD degeneration, vacuum phenomenon, IVD instability, IVD pain and pressure, and complicated with spinal stenosis	2	M (0) F (2)	69 (± 2)	*NA*	None	2

A tabular overview of all identified published clinical studies and their design characteristics

AF annulus fibrosus, *LBP* low back pain, *IVD* Intervertebral disc

[a] Patient numbers represent the number of participants from which outcome parameters are reported in the referenced publication. The final included population for the trial might be larger

[b] Duration of the final follow-up in years for which outcome parameters are presented in the referenced publications

Table 2 Overview assessed parameters for each clinical trial for pain, disability, general health, and IVD features

Author	Year		VAS pain score	NPS/ NRS	PPI	Legg numbness	SF McGill pain	Dallas Questionnaire	LBP subscale score	ODI score	FRI	JOA LBP score	QUEBEC scale	Flexion
Centeno	2017	[19]		x							x			
Comella	2017	[20]	x		x		x	x		x				x
Coric	2013	[21]		x						x				
Elabd	2016	[22]												
Haufe	2006	[23]	x											
Kumar	2017	[24]	x							x				
Meisel	2006	[25]	x							x			x	
Mochida	2015	[27]							x			x		
Noriega	2017	[28]	x							x				
Orozco	2011	[29]	x							x				
Pang	2014	[30]	x							x				
Pettine	2014	[31]	x							x				
Tschugg	2017	[34]												
Yoshikawa	2010	[35]	x			x						x		
			Pain							Disability				

Author	Self-reported strength	Self-reported mobility	SF-36	SF-12	BDI	SANE	PROLO	Return to work	Quality of life questionnaire	Hydration	IVD height	Bulge/protrusion size	Pfirrmann classification
Centeno						x						x	
Comella				x	x								
Coric			x							x	x		
Elabd	x	x							x		x	x	
Haufe													
Kumar			x							x	x		x
Meisel			x				x			x	x		
Mochida								x		x			x
Noriega				x						x	x		x
Orozco			x							x	x		
Pang										x			
Pettine													x
Tschugg													
Yoshikawa										x			
			General health							MRI and X-ray			

BDI Beck depression index, *FRI* functional rating index, *IVD* intervertebral disc, *JOA* Japanese orthopedic association, *LBP* low back pain, *NPS/NRS* numerical rating score, *ODI* Oswerty disability index, *PPI* present pain index, *SF* short form; *VAS* visual analogue scale

Table 3 Overview of clinical study outcomes

Author	Ref	Year	Mode	Cell type	Control	Patient	SAE	Summarized outcomes	
Centeno et al.	[19]	2017	Autologous	Mesenchymal stem cells	None	33	Disc herniation ($n = 1$)	General:	SANE score improved for majority of patients but shows decrease in improvement trend after 3 years
								Pain:	Significant improvement NPS from 3- to 6-year transplant, but shows deteriorating trend after 1 year
								Disability:	Significant improvement FRI from 3 to 6 years post-transplant, but trend of worsening from 5 years
								IVD:	Average of 23% reduction in 17/20 patients bulge size
								General:	2 patients discontinued the study and underwent separate surgical intervention
Comella et al.	[20]	2017	Autologous	Stromal vascular faction	None	15	None observed	Pain:	Trend of reduction in pain VAS
								Pain:	Trend of PPI discomfort reduction
								Disability:	ODI average change showed small trend of improvement
								Disability:	BDI average change showed maintenance trend
								Disability:	Small improvement trend in flexion values
								General:	DALLAS Questionnaire demonstrated mixed results
								General:	SF-MPQ revealed slight significant improvement
								General:	SF-12 revealed slight significant improvement
Coric et al.	[21]	2013	Allogeneic	Chondrocytes (Juvenile)	None	15	None observed	Disability:	Significant reduction in ODI score
								Pain:	Significant reduction in NRS
								General:	Significant improvement in SF-36 scores
								IVD:	MRI observation showed improvement for majority of patients
Elabd et al.	[22]	2016	Autologous	Mesenchymal stem cells	None	5	None observed	IVD:	Disc height assessment revealed maintenance or mild decrease
								IVD:	4/5 patients showed decreased protrusion size, 1 showed increase in size
								General:	Quality of life questionnaire revealed trend of improvement
								Disability:	Reported mobility improved for 80% of patients
								Disability:	Reported patients strength improved of all patients
Haufe and Mork	[23]	2006	Autologous	Hematopoietic stem cells	None	10	*Unspecified*	Pain:	No improvements reported
								General:	After 1 year, 8 patients continued to surgical intervention
Kumar et al.	[24]	2017	Autologous	Mesenchymal stem cells	None	10	None observed	Pain:	Significant reduction in VAS
								Disability:	Significant reduction in ODI
								IVD:	Disc height by X-ray did not show any reduction
								IVD:	No deterioration observed by Pfirrmann classification
								IVD:	Mixed outcomes for MRI determined IVD hydration

Table 3 (continued)

Author	Ref	Year	Mode	Cell type	Control	Patient	SAE	Summarized outcomes	
Meisel et al.	[25] [26]	2006	Autologous	Intervertebral disc chondrocytes	No transplant (discectomy only)	12 (Co-n:16)	None observed	Pain:	Trend of improvement in VAS, trend of enhanced improvement to control
								Disability:	Trend of enhanced improvement for OPDQ, trend of enhanced improvement to control
								IVD:	Significant improvement in IVD hydration compared to control
								IVD:	IVD height, assessed by MRI, was maintained
Mochida et al.	[27]	2015	Autologous	Reactivated nucleus pulposus cell	None	9	None reported	Disability:	JOA questionnaire revealed strong improvement trend
								Pain:	LBP subscale showed trend of improvement
								General:	All participants were able to return to work
								IVD:	Slight improvement in Pfirrmann classification
								IVD:	Maintenance in MRI determined hydration values
Noriega et al.	[28]	2017	Allogeneic	Mesenchymal stem cells	Paravertebral musculature anesthetic injection	24	None observed	Disability:	ODI significantly reduced for MSC treated disc
								Disability:	ODI showed further deterioration for control discs
								Pain:	VAS significantly decreased for MSC, similar trend observed for control
								IVD:	Disc height decreases, but trend is slower for MSC treated group
								IVD:	MRI determined IVD hydration stabilized for both conditions
								IVD:	Pfirrmann classification reduced for MSC and significantly increases for control group
								General:	SF-12 showed trend of improvement for both conditions
Orozco et al.	[29]	2011	Autologous	Mesenchymal stem cells	None	10	None observed	Pain:	Lumbar pain VAS showed significant reduction and was maintained throughout
								Pain:	Sciatic pain VAS showed significant reduction and was maintained throughout
								Disability:	ODI showed significant reduction and was maintained throughout
								General:	SF-36 demonstrated significant reduction
								IVD:	Disc height was maintained
								IVD:	MRI determined IVD hydration showed significant improvement
Pang et al.	[30]	2014	*unspecified*	Umbilical cord mesenchymal stem cells	None	2	None observed	Pain:	VAS showed trend of improvement
								Disability:	ODI showed trend of improvement
								IVD:	MRI determined hydration showed maintenance or improvement

Table 3 (continued)

Author	Ref	Year	Mode	Cell type	Control	Patient	SAE	Summarized outcomes	
Pettine et al.	[10] [31] [32]	2014	Autologous	Bone marrow concentrates	None	26	None observed	Pain:	VAS was significantly reduced at 3 m and maintained for 3 years
								Disability:	ODI was significantly reduced at 3 m and maintained for 3 years
								IVD:	8/20 patients showed improvement in Pfirrmann grade, rest maintained classification
								General:	6/26 patients discontinued cell therapy for surgical intervention
Tschugg et al.	[33] [34]	2017	Autologous	Intervertebral disc chondrocytes	Only carrier: Albumin, hyaluronic acid gel (placebo)	12 (Con 8)	Reherniation ($n = 1$)		No efficiency outcomes reported
Yoshikawa et al.	[35]	2010	Autologous	Mesenchymal stem cells	None	2	None observed	IVD:	Vacuum phenomenon improved in all patients
								IVD:	MRI determined IVD hydration was reported to be improved
								Pain:	VAS improved for both patients
								Disability:	JOA questionnaire revealed improvement trend
								Pain:	Leg numbness was alleviated

A collective overview of summarized outcomes from each publication

BDI Beck depression index, *FRI* functional rating index, *IVD* intervertebral disc, *JOA* Japanese orthopedic association, *LBP* low back pain, *NPS/NRS* numerical rating score, *ODI* Oswerty disability index, *PPI* present pain index, *SAE* serious adverse event, *SF* short form, *VAS* visual analogue scale

Table 4 Overview of product and treatment characteristics

Author		Ref	Year	Method	Gauge	Disc levels	Mode	Cell type	Cell source
Centeno	et al.	[19]	2017	Intradiscal	*Unspecified*	*Unclear*	Autologous	Mesenchymal Stem Cells	Bone marrow
Comella	et al.	[20]	2017	Intradiscal	*Unspecified*	*Unspecified*	Autologous	Stromal vascular faction	Adipose tissue
Coric	et al.	[21]	2013	Intradiscal	22G	L3/4 L4/5 L5/S1	Allogeneic	Chondrocytes	Juvenile cadaveric articular cartilage
Elabd	et al.	[22]	2016	Intradiscal	22G	L5/S1 L4/5	Autologous	Mesenchymal Stem Cells	Bone marrow
Haufe & Mork		[23]	2006	Intradiscal	22G	*Unspecified*	Autologous	Hematopoietic stem cells	Pelvic bone marrow
Kumar	et al.	[24]	2017	Intradiscal	22G	L4/5 L5/S1	Autologous	Mesenchymal Stem Cells	Adipose tissue
Meisel	et al.	[25] [26]	2006	Intradiscal	*Unspecified*	*Unspecified*	Autologous	Intervertebral disc chondrocytes	unspecified
Mochida	et al.	[27]	2015	Intradiscal	21G	L4/5 L5/S1	Autologous	Reactivated nucleus pulposus cell	Degenerated IVD, undergoing fusion treatment
Noriega	et al.	[28]	2017	Intradiscal	*Unspecified*	L1-L2, L2-L3, L3-L4, L4-L5, L5-S1	Allogeneic	Mesenchymal stem cells	Bone marrow
Orozco	et al.	[29]	2011	Intradiscal	*Unspecified*	L4/5 L5/S1	Autologous	Mesenchymal Stem Cells	Iliac crest
Pang	et al.	[30]	2014	Intradiscal	*Unspecified*	L3/4 L4/5	*Unspecified*	Umbilical Cord Mesenchymal stem cells	Umbilical cord
Pettine	et al.	[10] [31] [32]	2014	Intradiscal	22G	L4/5 L5/S1	Autologous	Bone marrow concentrates	Iliac crest
Tschugg	et al.	[33] [34]	2017	Intradiscal	*Unspecified*	L3/4 L4/5 L5/S1	Autologous	Intervertebral disc chondrocytes	Autologous IVD explants from sequestrectomy
Yoshikawa	et al.	[35]	2010	*Unspecified*	*Unspecified*	L2/3 L3/4 L4/5	Autologous	Mesenchymal stem cells	Bone marrow

Table 4 (continued)

Author	Notes	Transplant mode	Carrier	Volume	Cells density (× 10^6)	Control groups	Notes
Centeno	–	Suspension	10–20% Platelet lysate, PBS	1–3 mL	1.73–45	None	Additional triple autologous platelet lysate injection. Depending on rate of improvement, multiple transplants were given.
Comella	–	Suspension	Autologous platelet rich lysate	1 mL	10–60	None	–
Coric	–	Encapsulated	Fibrin	1–2 mL	10–20	None	–
Elabd	Cultured under hypoxia	Suspension	Platelet lysate	0.25–1 mL	31 (± 14)	None	–
Haufe & Mork	–	*Unspecified*	*Unspecified*	1 mL	*Unspecified*	None	
Kumar	High (40 × 10^6) and Low dose (20 × 10^6)	Encapsulated	Tissuefill (hyaluronic acid derivative)	2 mL	40 or 20	None	–
Meisel	–	Suspension	*Unspecified*	Unspecified	*Unspecified*	No transplant (discectomy only)	Transplant performed 12 weeks post-discectomy
Mochida	Co-cultured with autologous MSCs	Suspension	PBS	702 μL	1	None	–
Noriega	–	Suspension	PBS	2 mL	25	Paravertebral musculature anesthetic injection	–
Orozco	–	Suspension	0.5% albumin, 5 mM glucose, Ringer-lactate solution	Unspecified	10 (± 5)	None	–
Pang	–	Suspension	*Unspecified*	Unspecified	*Unspecified*	None	–
Pettine	–	Suspension	*Unspecified*	2–3 mL	121 (± 11)	None	Patients representing < 25% improvement in VAS or ODI, after 6 months; could receive second cell transplant
Tschugg	–	Encapsulated	Albumin, hyaluronic acid gel	0.5–2 mL	*Unspecified*	Only carrier: Albumin, hyaluronic acid gel (placebo)	Carrier contains culture medium, serum, chondroitin sulfate, insulin, BMP2, and ascorbate. Carrier polymerized by polyethylene glycol
Yoshikawa	–	Grafted	Pelnac collagen sponge	~ 0.54 mL	*Unclear*	None	–

A tabular overview of the transplantation procedures and cellular product for each included clinical study

BMP2 bone morphogenetic protein-2, *IVD* intervertebral disc, *MSC* mesenchymal stem cells, *ODI* Oswerty disability index, *PBS* phosphate-buffered saline, *VAS* Visual analogue scale

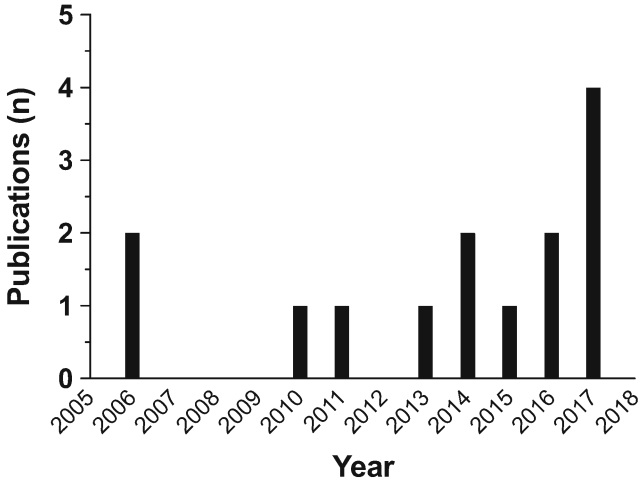

Fig. 2 A graphic representation of the number of novel in-human studies and the year they were published. A trend of increased publication rate is observed. Graph made by GraphPad Prism (GraphPad Inc., San Diego, California, USA)

One study also assessed leg numbness [35] and one study applied Present Pain Index (PPI) outcomes [20]. Mochida et al. [27] applied an LBP subscale scoring system, while Comella et al. [20] also included Short Form (SF) McGill and Dallas pain questionnaires. Disability scores were assessed in all studies, except for the study by Tschugg et al. [33, 34], Elabd et al. [22], and Haufe et al. [23]. Elabd et al. [22] does not include a direct assessment of disability, but more generally describes self-reported improvement of strength and mobility. Most studies applied Oswestry LBP questionnaires and reported Oswestry Disability Index (ODI) scores to evaluate disability alteration. (Tables 2 and 3) Additionally, studies applied alternative disability assessments such as the Japanese Orthopedic Association (JOA) LBP scoring system, QUEBEC back pain disability scale, and Functional Rating Index (FRI) were applied. Finally, general health and quality of life assessment were performed with a large variety of studies applying different questionnaires (Tables 2 and 3), with Short Form (SF)-12 or SF-36 questionnaires as the most commonly applied assessments. Although patient reported outcome measures are commonly accepted as relevant clinical outcomes, there is a need for more objective and quantifiable parameters [17, 18, 36]. In particular, as the majority did not include a (placebo) control group, a sincere caveat for interpreting the presented values, as the placebo phenomena has significant effects on outcome parameters [37, 38]. Nevertheless, designing an appropriate placebo control and managing the associated risks remains a point of debate. Interestingly, Comella et al. [20] appears to include the evaluation of lumbar and pelvic flexion as quantifiable outcome parameter, although within the study, the definitions of this assessment were not well-defined. Conceivably, new advances in biomarkers, gait analysis, imaging techniques, and wearable devices might provide more quantifiable non-invasive outcome parameters for future clinical studies, and emphasis should be placed on their development, assessment, and standardization [39–42].

On the contrary, efficacy should also be assessed by the capacity to restore structural and biomechanical features of the afflicted IVD. Commonly assessed features are hydration values and Pfirrmann grade classification as assessed by MRI or disc height assessed by radiographic imaging. Both outcome parameters indicate the efficacy of tissue regeneration by the product, although these observations do require skepticism as MRI classification and histology has been suggested to lack direct relationship. [43] Moreover, changes in hydration values are not the sole features associated with IVD degeneration, and aspects such as cell clustering, AF fissures, and ECM composition are not yet observable. Moreover, potential new and promising developments in imaging techniques would likely still require timely and intensive validation, standardization, and clinical adaptation to become expected parameters for clinical trials. [39–41]

The cellular product considerations

Cell type and source

Cell transplant efficacy could either be accomplished by paracrine signaling of the de novo cells to stimulate endemic cells, or by actively participating in ECM production and homeostasis [17]. MSC [44] and juvenile NP cells [45] are able to reactivate degenerated NP cells, a phenomenon applied by Mochida et al. [27] to enhance their NP cell product. Moreover, animal studies have demonstrated the survival and direct contribution to de novo ECM [46, 47]. The therapeutic cells will need to uphold their regenerative potency in a relatively acidic, hypoglycemic, osmolar, and hypoxic environment and under strident biomechanical conditions, exacerbated by degeneration, as EP perfusion is further restricted, hydration is compromised, and secretion of catabolic factor is intensified [48, 49]. Therefore, it is crucial to select cell populations able to (i) survive within these conditions, (ii) thrive and contribute directly or indirectly to anabolic ECM production, and (iii) maintain their anabolic features long-term within the IVD. A variety of studies are exploring pre-conditioning of MSC prior to transplantation [50–52]. Elabd et al. [22] applied such strategy by pre-culturing their allogeneic MSCs under hypoxic conditions. Although the MSCs have shown able to take on a more chondrogenic NP-like phenotype [50–52], the true nature of such cells remains elusive. A particular issue, as the conditions applied are generally associated with chondrogenesis, while NP-ECM is distinctive to other cartilage tissue (e.g., proteoglycan and type II collagen ratios [53]). IVD-derived cells would arguably pose an optimal cell source, as

they are inherently predisposed to thrive in the IVD and create an appropriate ECM. Nevertheless, their low cell yield and inaccessibility are considered a sincere hurdle [54, 55]. Moreover, available IVD tissue is scarce and oten compromised by disease, age, or trauma [54, 55]. This could potentially be surmounted by revitalizing approaches, to stimulate the afflicted NP cells [27, 44].

The reported clinical studies apply a variety of different cell types and sources (Table 4). The most frequently applied cell is the MSC, with 11 separate studies applying this cell type. MSCs were harvested from either the umbilical cord [30], bone marrow [10, 19, 22, 23, 28, 29, 31, 32, 35], or adipose tissue [20, 24]. The other cell types applied were articular-cartilage-derived chondrocytes [21] and IVD-derived cells [25–27, 33, 34]. All studies applying MSC appeared safe and only one study reported SAE [19] (Table 3). Efficacy outcomes of MSC treatment showed heterogenous results, with studies presenting significant improvement in pain and disability scores, or a trend of improvement (Table 3). However, Haufe et al. [23] reported no observable improvements for their transplanted MSC, and both Pettine et al. [10] and Centeno et al. [19] reported patients (respectively 6/26 and 2/33) discontinuing participation to undergo regular surgical treatment. From the current overview (Table 3), it becomes evident that overall, MSC treatment appears able to induce at minimum a trend of improvement in pain, disability, and quality of life assessment. However, more mixed results are observed for regenerative features as assessed by radiographic assessments. Here, the more quantitative measures show mixed trends, presenting both improvements, but also maintenance or reduced deterioration of IVD features. For chondrogenic IVD or cartilage-derived cells, all studies showed improvement in pain and disability outcomes and were able to observe a trend of improvement in MRI assessments, with only Mochida et al. [27] reporting maintenance of hydration values within their cohort. A recent meta-analysis by Wu et al. [56] including six of the here discussed 14 studies [21, 25, 27, 29–31] reported a significant collective improvement for cell transplantation on both numerical pain and ODI scores. Moreover, a meta-regression analysis did reveal a significant preference for MSC studies [29–31], as opposed to chondrogenic cells [21, 25, 56]. It is however clear that both cell types show initial efficacy in alleviating pain and promoting maintenance or recovery of IVD features. Optimization of the cellular products and imperative large controlled clinical studies will likely provide needed insight in the potential and preferential cell type suitable for specific patients and indications.

Additionally, allogeneic and autologous modes of transplantation are practical considerations for the product development and safety. The majority of studies reported applied an autologous approach for MSC [10, 19, 20, 22–24, 29, 31, 32, 35] or cartilage-derived cell [26, 27, 33, 34] products. Although, an autologous approach has the benefit of reduced risk of immunogenicity. Concerns remain with additional procedural costs and time (that will likely decrease commerciality), as well as additional required surgeries, harvest site morbidity, and limitations based on patient's disease and age status [57]. The allogeneic cell studies [21, 28, 30] reported no observable SAE to their transplantation products. Similarly, large animal studies have suggested an immune-deprived environment within the IVD [46]; however, to what level of IVD degeneration this privileged condition is maintained, remains undetermined. Allogeneic transplantation approaches have the benefit of allowing extensive evaluation of quality and safety of batches and could provide an off-the-shelf (OTS) product. Hiraishi et al. [46] reported that injecting NP cells directly from their cryopreserved OTS state is an effective and safe strategy within a canine model. Such OTS strategies enable cost reduction and batch profiling and increase ease of use for practitioners.

Cell density

The current reports apply a range of one million to 120 million cells per disc (Table 4). A variety of studies did not specify the final transplanted density [23, 25, 26, 30, 33–35]. Cell dosage can substantially influence the potency of the cell product [46, 58]. A large concentration of de novo cells could compete for already limited nutrients, potentially inducing more cell death and senescence, further skewing the imbalance toward degeneration. Pettine et al. [10, 31, 32], applying bone marrow concentrates, assessed how the number of colony forming units (CFU) in their transplant affected the clinical outcomes. Patients receiving transplant of > 2000 CFU-F/mL revealed significantly reduced VAS pain scores compared to the patients receiving < 2000 CFU-F/mL. Elabd et al. [22] also reported a positive trend, in which an increased number of transplanted MSC exhibited higher scores of "overall improvement." On the other hand, work by Kumar et al. [24] applying 20 million ($n = 5$) and 40 ($n = 5$) million cells, did not observe a significant difference between the two dosage groups.

Carrier and transplantation methods

All recognized clinical studies applied intradiscal transplantation, by a needle puncture through the AF to enable administration (Table 4). Annular puncture is able to induce degeneration and could create a weak spot in the AF [59]. In this review, all identified publications applied a 21G or 22G needle. Interestingly, a recent goat study revealed that 22G puncture did not result in degenerative changes observed in radiography or histology [60]. Additionally, high IVD pressures will force newly introduced and non-adhering entities outwards. In an IVD with compromised AF or by the puncture artifact, leakage is likely to occur. Product leakage could result

in adverse effects at other sites, e.g., osteophyte formation [61]. Although, the majority of studies applied cells in suspension cell, none reported SAE related to cell leakage (Table 4). Nevertheless, to minimize these risks, patients are ideally selected on an intact AF, or augmentation of AF defect is included. Adhering or non-viscous carriers could be incorporated to encapsulate or graft the therapeutic cells. The additional benefits of applying carriers are improved distribution throughout the IVD. Moreover, the carrier could be designed to promote desirable cell behaviour. At current, clinical studies have applied fibrin [21], Pelnac collagen sponge [35], or hyaluronic acid derivatives [24, 33, 34] (Table 4). Data does not provide sufficient evidence to make a conclusive statement, if carriers enhance the treatment's potential. Finally, new approaches of IVD cell delivery are being explored, e.g., by transpedicular approach [62] or utilizing cellular homing after transplantation into adjacent vertebrae [63]. These strategies remain in early stages of pre-clinical development.

Patient selections and customization

Selection of appropriate patients presenting suitable indications for the assessment of cell products is an imperative consideration for the trial design. Potential suitable indications could include degenerative disc disease, discogenic pain, adjacent segment disease, and post-discectomy syndrome and might be curative or preventative in nature. The state of the IVD should ideally be assessed, to ensure a suitable IVD environment for product implementation. For example, an intact AF and a non-calcified EP are likely desirable in these early stages of development and were common indications used in the recognized trials (Table 1). Otherwise, the IVD should present distinguishable deterioration to enable observations of accomplished regeneration. Generally, the included studies applied MRI and observed IVD degeneration ranging from Pfirrmann grade III-IV, with patients presenting refractory LBP for three to six months after conservative treatments and excluded patients presenting other spinal abnormalities. Moreover, patient selection is ideally focused on a very specific and small-grouped indication, in order to reduce heterogenicity. It will be beneficial to have specific quantifiable measures that could help assess the efficacy of their product. Nevertheless, new advancements are likely needed to allow non-invasive assessment of pain, disability, and tissue regeneration.

Realization and commercialization

From basic research to a product in the clinician's toolbox is a complex, timely, and costly undertaking [64]. From concept to final stages of a clinical trial, it is crucial for researchers to contemplate the potential application as a realized commercial product. Cell therapy for IVD regeneration holds great promise, due to the possibility of percutaneous transplantation, offering a potentially low-cost, low-risk treatment that is postulated to offer long-term benefits for a large population of patients with minimal risks. Nevertheless, although new cell products might show effective and safe in the development phase, common obstacles could hinder market translatability, provoking limited regenerative products being authorized for clinical application [64].

In the early stages of development, the researchers should consider the protection of their ideas and products by patent, prior to presenting their results to the public as a research article, conference presentation, etc. Intellectual property (IP) publicly presented prior to filing for patent is likely unable to obtain a protected IP status, critically hindering potential market translation. Moreover, researchers should be mindful about the product design and procedures. Complicated technologies, involving multiple processes and components, will hinder the chance of success, by increasing the costs and requirement of safety and efficacy assessments. Thereby, consider minimizing or substituting expensive compounds and applying already clinically approved alternatives. Also, be aware of local regulations for required manufacturing and clinical practices the product will have to comply to [64]. It is therefore recommended to involve business and regulatory professionals in early stages of development. For successful translation, consider a specific target patient population and be aware of the competing technologies, which new therapies have to challenge on basis of efficacy and costs. These deliberations are crucial, for enabling and accelerating development of safe and effective regenerative therapies in the benefit of the patients.

Conclusion

Cell therapy for IVD regeneration offers a low-risk, low-cost strategy, with potentially long-term effects and are highly anticipated treatments for a large cohort of patients. Current published work on in-human clinical trials indicates that cell transplantation is an overall safe approach. Current evidence does show an initial trend of beneficial outcomes favoring cell therapy. Nevertheless, the studies involve highly heterogenic transplantation approaches, patient cohorts, and cell products while sample sizes are low and present limited outcome parameters. Therefore, results should be interpreted with caution. Large, placebo-controlled clinical trials will be required and are the only evidence-based approach to define a cell therapy effective.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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