Biologics in Joint Preservation

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Disclosures

- None

Objectives

- Discuss current biologics available for joint preservation
  - Focus on knee OA
- Review literature on biologic therapy for joint preservation
- Discuss current regulatory issues surrounding biologic therapy
- Discuss future directions of biologic therapy

- **Background**
- Types of biologic therapies
- Current Research
- Controversial issues
- Summary

Why is this important

- Degenerative disease of the MSK system is an epidemic
  - Includes OA, tendinopathy, and degenerative disc disease

- Biologics are being marketed for joint preservation across the country
  - In many cases the economics are outpacing the science

- Biologic therapies have the potential to reverse the effects of aging
  - Slow or reverse cellular destruction and loss of tissue function.
  - Reduce pain and potentially defer surgical intervention

Biologics

- Term used to describe therapeutics derived from human tissue

  - Platelet Rich Plasma (PRP)
  - Autologous conditioned serum (ACS)
  - Mesenchymal Progenitor Cells “Stem Cells” (MSC)
  - Micro-fragmented Fat
  - Stromal Vascular Fraction (SVF)
  - Amniotic Membrane Tissue or Fluid

Biologics

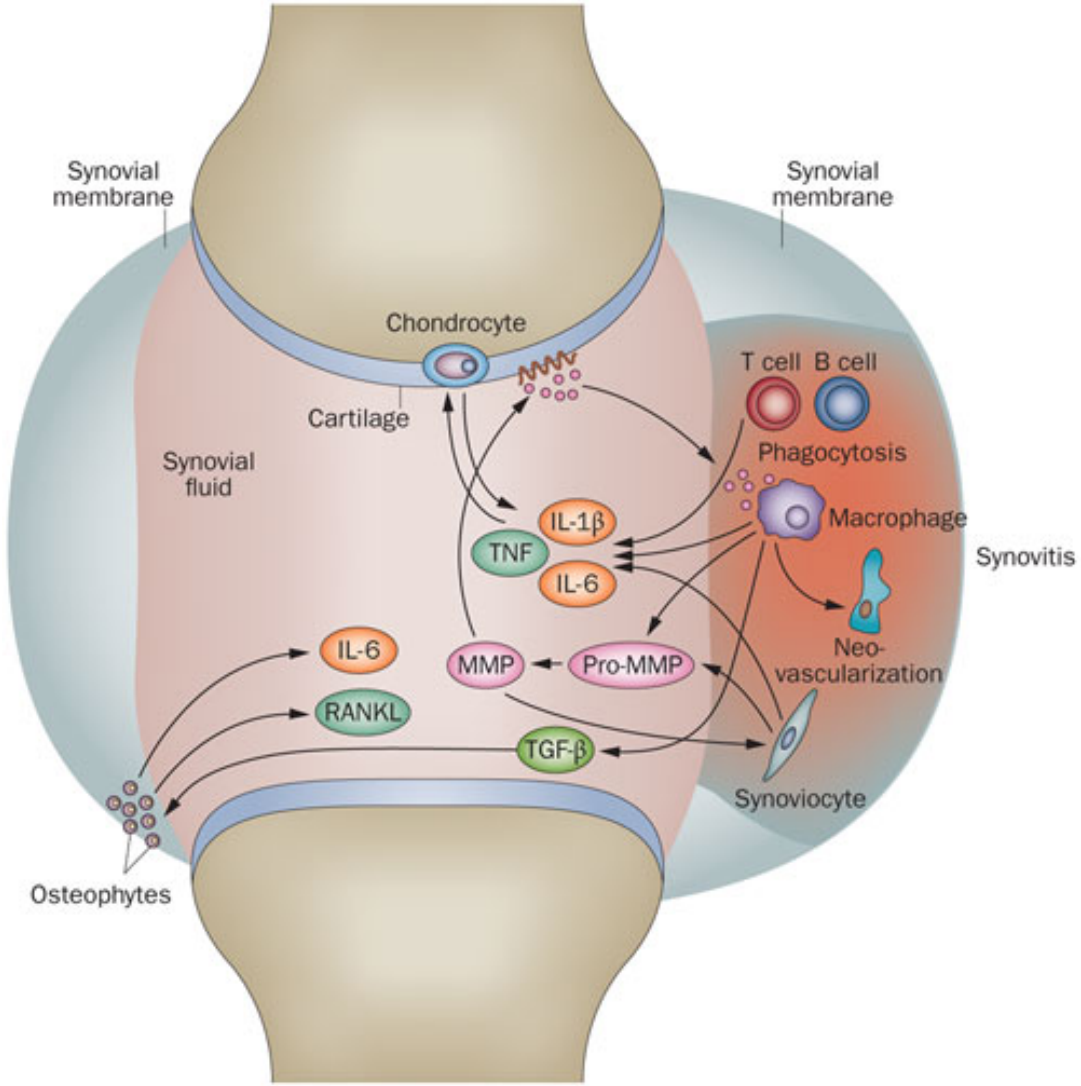
- Thought to confer benefits through immunomodulation and trophic activity.
  - Attenuation of inflammation within the injured tissue
  - Release of growth factors and other regulatory proteins

- Can improve tissue preservation and repair?

Basic Science of OA

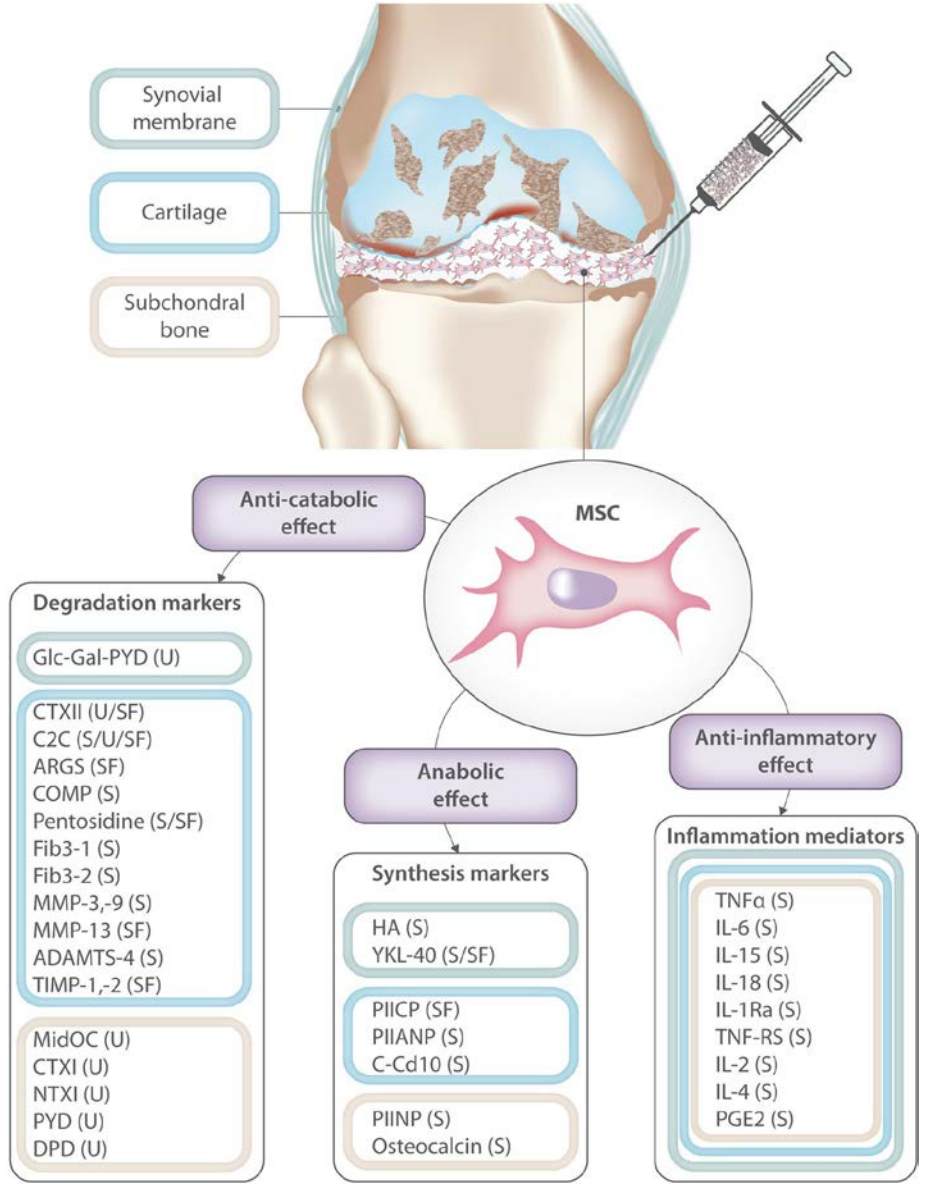
- Osteoarthritis if a complex multi-factorial process

- We are still understanding what is actually happening at a cellular level



Stem Cells

- Anti-inflammatory, anti-catabolic, and trophic abilities.



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Platelet Rich Plasma

- Supra-physiologic concentration of platelets
- PRP has been shown to promote cell recruitment, proliferation, and angiogenesis
- Current applications vary widely (arthritis and tendonitis)

PRP: Formulations

- No standardized description of PRP
  - Many companies selling many different formulations

- What seems to matter
  - Platelet amount
  - Number of WBCs

Basic science: Why the platelet

Alpha granule contents:

Growth Factor	Function
platelet-derived growth factor (PDGF)	Stimulates cell replication, angiogenesis, mitogen for fibroblasts
vascular endothelial growth factor (VEGF)	Angiogenesis
transforming growth factor beta-1 (TGF-b1)	Regulates balance between fibrosis and myocyte regeneration
insulin-like growth factor-1 (IGF-1)	Stimulates myoblasts and fibroblasts, mediates growth and repair of skeletal muscle
epidermal growth factor (EGF)	Proliferation of mesenchymal and epithelial cells, potentiation of other growth factors
basic fibroblast growth factor (bFGF)	Stimulates proliferation of myoblasts, angiogenesis

Autologous Conditioned Serum (ACS)

- Acellular treatment and is produced by incubating venous blood in a specialized syringe
  - No preservatives like PRP

- Blood cells produce anti-inflammatory cytokines including IL-1 receptor antagonist (IL-1Ra), IL-4, and IL-10

Mesenchymal Progenitor Cells

- Cells derived from mesenchymal tissues and arise from pericytes.
- Multilineage potential for their ability to differentiate into osteocytes, adipocytes, chondrocytes, tenocytes
- In current therapies there are very little to no “pluripotent stem cells”
  - Can only produce mesenchymal tissue

Mesenchymal Progenitor Cells

- Can be adipose derived or bone marrow derived

- Initially thought to reconstitute injured tissues.
  - Recent research has shown the effects of MSCs have been reconsidered

Fat Tissue Derived Biologics

Micro-fragmented Fat

- Adipose-tissue derivative prepared via mechanical breakdown of fat tissue into tiny particles to release cells from the extracellular matrix.
  - No collagenase treatment or culture expansion is involved during its preparation process.

- Product is rich in MSCs, preadipocytes, fibroblasts, and macrophages

Fat Tissue Derived Biologics

Stromal Vascular Fraction

- Obtained from adipose tissue that is digested with collagenase.
  - Mechanical agitation may be used instead
- Adipocytes and free fat are then removed after centrifugation.
- Population of cells includes MSCs along with macrophages, red blood cells, T-cells, preadipocytes, pericytes, fibroblasts, and endothelial cells.

Amniotic Tissue

- Amniotic Fluid possess immunomodulatory properties without the ethical issues of embryonic cells

- CD 117 cells can differentiate into all germ layers
  - Non-tumorogenic
  - More primitive in the first trimester

- Currently 7 or more companies offering amniotic fluid
  - Very little clinic human data supporting their use

Amniotic Tissue

- Amniotic Membrane is a thin and flexible placenta-derived membrane

- Biologically active amniotic membrane compounds include MSCs, cytokines, HA, growth factors, and other proteins.

- Numerous formulations
  - Cryopreserved amniotic membrane product
  - Cell-free dehydrated amnion/chorion membrane allograft.

- Background
- Types of biologic therapies
- **Current Research**
- Controversial issues
- Future directions

PRP: Pre-Clinical Data

- Chondrocytes Increase secretion of anti-inflammatory cytokines when cultured with PRP
- PRP induces synovial cells to produce endogenous HA
- PRP exhibits potential to stimulate chondrogenic differentiation and metabolism (collagen synthesis); migration and proliferation of MPCs.

Efficacy of platelet-rich plasma injections in osteoarthritis of the knee: a systematic review and meta-analysis

Augustinus B M Laudy,[1,2] Eric W P Bakker,[2] Mark Rekers,[3] Maarten H Moen[4,5]

Table 1 Details of the used PRP compilation and Mishra classification of PRP

References	Injections (N)/interval (weeks)/volume (mL)	Spinning approach	White cells count	Activation	Platelet concentration	Type PRP (Mishra classification)
Vaquerizo *et al*[36]*	3/2/8	Single spinning	–	+	<5×baseline	4B
Patel *et al*[37]*	1(2)/–(3)/8	Single spinning	–	+	<5×baseline	4B
Filardo *et al*[38 44]*	3/1/5	Double spinning	+	+	5×baseline	2A
Cerza *et al*[39]*	4/1/5.5	Single spinning	–	–	>5×baseline	3A
Sánchez *et al*[40]*	3/1/8	Single spinning	–	+	<5×baseline	4B
Say *et al*[41]	1/–/2.5	Single spinning	–	+	<5×baseline	4B
Spaková *et al*[42]	3/1/3	3 spinnings	+	–	<5×baseline	1B
Li *et al*[43]	3/3/3.5	NA	NA	+	NA	NA
Filardo *et al*[23]	3(3)/3(3)/5(5)	Single vs double spinning	– (+)	+(+)	<5×baseline	4B (2B)
Kon *et al*[16 45]	3/2/5	Double spinning	+	+	>5×baseline	2A

Type 1 PRP: increased white cells count and no activation; type 2 PRP: increased white cells count and activated; type 3 PRP: minimal/no white cells count and no activation; type 4 PRP: minimal/no white cells count and activated.
A: contains an increased platelet concentration at or above five times baseline (extracted venous blood).
B: contains an increased platelet concentration less than five times baseline (extracted venous blood).

Platelet-Rich Plasma Versus Hyaluronic Acid in the Treatment of Knee Osteoarthritis: A Meta-analysis of 26 Randomized Controlled Trials

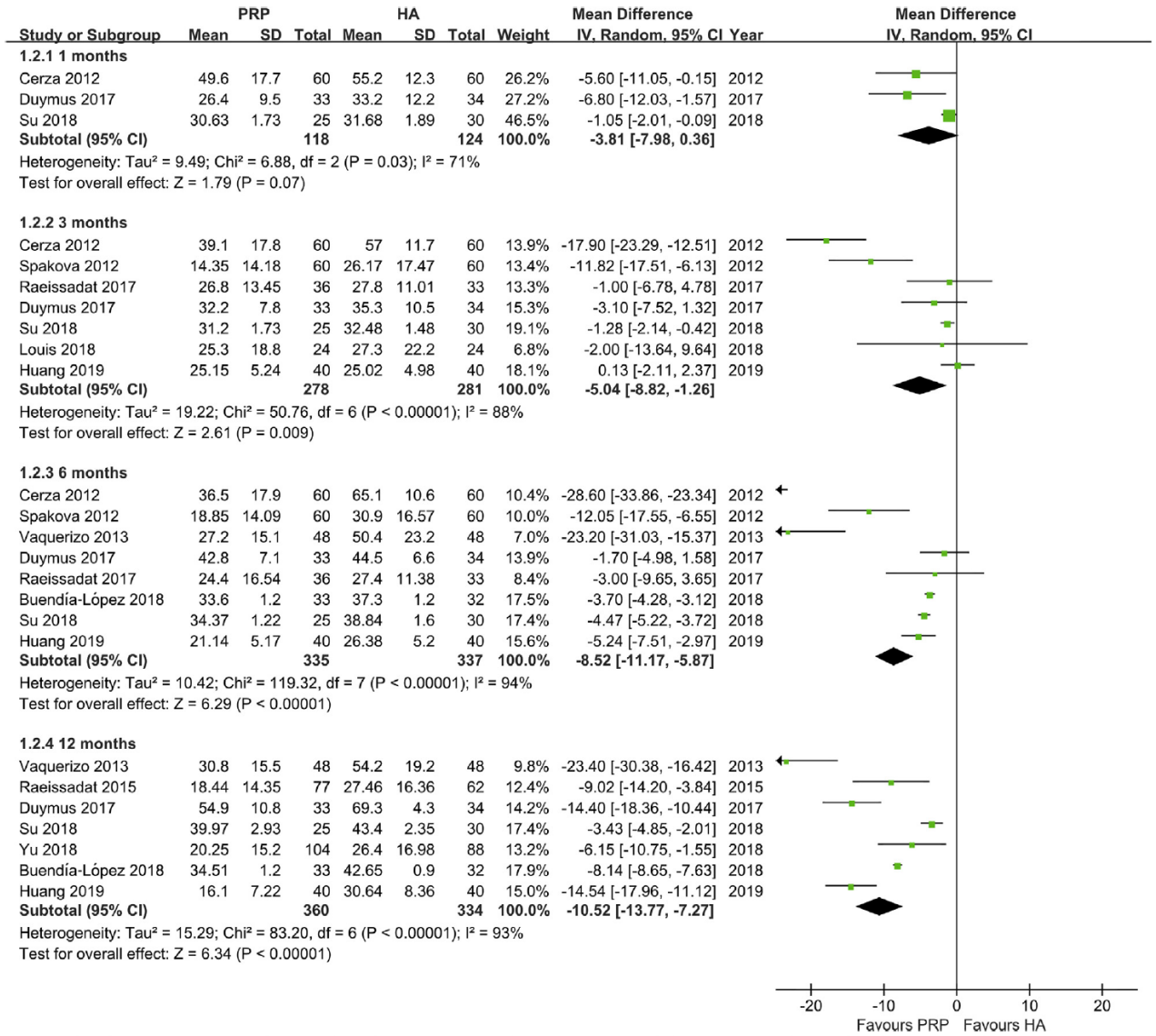
Jixiang Tan, M.D., Hong Chen, M.D., Lin Zhao, M.D., and Wei Huang, M.D.

- 2430 patients

- PRP group had better PROs compared to HA group at 6 and 12 months.
    - WOMAC, IKDC, VAS
    - no significant difference in adverse events

- Conclusions: For the nonsurgical treatment of Knee OA, compared with HA, PRP could significantly reduce patients' pain and improve function.

- PRP outperforms HA at 3, 6, and 12 months
- Average WOMAC improvement of 10 points



Study or Subgroup	PRP Mean	PRP SD	PRP Total	HA Mean	HA SD	HA Total	Weight	Mean Difference IV, Random, 95% CI	Year
1.2.1 1 months									
Cerza 2012	49.6	17.7	60	55.2	12.3	60	26.2%	-5.60 [-11.05, -0.15]	2012
Duymus 2017	26.4	9.5	33	33.2	12.2	34	27.2%	-6.80 [-12.03, -1.57]	2017
Su 2018	30.63	1.73	25	31.68	1.89	30	46.5%	-1.05 [-2.01, -0.09]	2018
Subtotal (95% CI)			**118**			**124**	**100.0%**	**-3.81 [-7.98, 0.36]**	
Heterogeneity: Tau² = 9.49; Chi² = 6.88, df = 2 (P = 0.03); I² = 71%									
Test for overall effect: Z = 1.79 (P = 0.07)									
1.2.2 3 months									
Cerza 2012	39.1	17.8	60	57	11.7	60	13.9%	-17.90 [-23.29, -12.51]	2012
Spakova 2012	14.35	14.18	60	26.17	17.47	60	13.4%	-11.82 [-17.51, -6.13]	2012
Raeissadat 2017	26.8	13.45	36	27.8	11.01	33	13.3%	-1.00 [-6.78, 4.78]	2017
Duymus 2017	32.2	7.8	33	35.3	10.5	34	15.3%	-3.10 [-7.52, 1.32]	2017
Su 2018	31.2	1.73	25	32.48	1.48	30	19.1%	-1.28 [-2.14, -0.42]	2018
Louis 2018	25.3	18.8	24	27.3	22.2	24	6.8%	-2.00 [-13.64, 9.64]	2018
Huang 2019	25.15	5.24	40	25.02	4.98	40	18.1%	0.13 [-2.11, 2.37]	2019
Subtotal (95% CI)			**278**			**281**	**100.0%**	**-5.04 [-8.82, -1.26]**	
Heterogeneity: Tau² = 19.22; Chi² = 50.76, df = 6 (P < 0.00001); I² = 88%									
Test for overall effect: Z = 2.61 (P = 0.009)									
1.2.3 6 months									
Cerza 2012	36.5	17.9	60	65.1	10.6	60	10.4%	-28.60 [-33.86, -23.34]	2012
Spakova 2012	18.85	14.09	60	30.9	16.57	60	10.0%	-12.05 [-17.55, -6.55]	2012
Vaquerizo 2013	27.2	15.1	48	50.4	23.2	48	7.0%	-23.20 [-31.03, -15.37]	2013
Duymus 2017	42.8	7.1	33	44.5	6.6	34	13.9%	-1.70 [-4.98, 1.58]	2017
Raeissadat 2017	24.4	16.54	36	27.4	11.38	33	8.4%	-3.00 [-9.65, 3.65]	2017
Buendía-López 2018	33.6	1.2	33	37.3	1.2	32	17.5%	-3.70 [-4.28, -3.12]	2018
Su 2018	34.37	1.22	25	38.84	1.6	30	17.4%	-4.47 [-5.22, -3.72]	2018
Huang 2019	21.14	5.17	40	26.38	5.2	40	15.6%	-5.24 [-7.51, -2.97]	2019
Subtotal (95% CI)			**335**			**337**	**100.0%**	**-8.52 [-11.17, -5.87]**	
Heterogeneity: Tau² = 10.42; Chi² = 119.32, df = 7 (P < 0.00001); I² = 94%									
Test for overall effect: Z = 6.29 (P < 0.00001)									
1.2.4 12 months									
Vaquerizo 2013	30.8	15.5	48	54.2	19.2	48	9.8%	-23.40 [-30.38, -16.42]	2013
Raeissadat 2015	18.44	14.35	77	27.46	16.36	62	12.4%	-9.02 [-14.20, -3.84]	2015
Duymus 2017	54.9	10.8	33	69.3	4.3	34	14.2%	-14.40 [-18.36, -10.44]	2017
Su 2018	39.97	2.93	25	43.4	2.35	30	17.4%	-3.43 [-4.85, -2.01]	2018
Yu 2018	20.25	15.2	104	26.4	16.98	88	13.2%	-6.15 [-10.75, -1.55]	2018
Buendía-López 2018	34.51	1.2	33	42.65	0.9	32	17.9%	-8.14 [-8.65, -7.63]	2018
Huang 2019	16.1	7.22	40	30.64	8.36	40	15.0%	-14.54 [-17.96, -11.12]	2019
Subtotal (95% CI)			**360**			**334**	**100.0%**	**-10.52 [-13.77, -7.27]**	
Heterogeneity: Tau² = 15.29; Chi² = 83.20, df = 6 (P < 0.00001); I² = 93%									
Test for overall effect: Z = 6.34 (P < 0.00001)									

Fig 4. Trials of PRP versus HA: forest plot of WOMAC total score. (CI, confidence interval; HA, hyaluronic acid; IV, inverse variance; PRP, platelet-rich plasma; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.)

Adipose derived tissue

TABLE 2. Studies assessing microfragmented fat and stromal vascular fraction

Authors, Year	Study Type	No. Patients (Joints)	Condition	Treatment	Volume/Dose	Outcomes
Russo et al., 2017[34]	Retrospective review	30 pts	Knee OA	MF	10–15 ml	VAS decreased by 24 points, Tegner Lysholm Knee by 31 at 12 mos of follow-up, IKDC-subjective and KOOS improved by 20 points; 1 patient had recurrent effusions in the first months.
Cattaneo et al., 2018[35]	Retrospective review	38 pts	Knee OA ± meniscal injury	Chondral shaving ± menisectomy and MF	10 ml	Improvement noted in all clinical scales, KOOS subscales and WOMAC at all time points for chondral shaving group only, mild decrease of effect in menisectomy group from 6 to 12 mos.
Hudetz et al., 2017[33]	Prospective open label	17 pts	Knee OA	MF	4–15 ml	Increase in GAG in cartilage (dGEMRIC), improved VAS score at 3, 6, and 12 mos
Panchal et al., 2018[32]	Prospective open label	17 pts (26 knees)	Knee OA, grade III–IV	MF	Not known	Significant improvements were noted in the mean values of NPRS, FXN, and LEAS at 6 wks, 6 mos, and 12 mos. The KSS significantly improved at 6 wks and 12 mos. No serious adverse events were reported.
Striano et al., 2018[36]	Prospective open label	18 pts	Shoulder OA	MF	4 ml intra-articular, 1–2 ml in other perilesional locations	NPRS and ASES improved at all time points, scores changed from 7.94 to 3.7 (NPS) and 33 to 66 (ASES) at 12 mos.

All show improvement from baseline in PROs but no cartilage restoration

No control group, small numbers

Hong et al., 2019[40]	Randomized self- controlled trial	16 pts	OA K-L II or III	SVF vs HA in each patient	4 ml	SVF-treated knees improved in VAS, WOMAC scores, and ROM at 12 mos of follow-up. In control group, all scores worsened from baseline to the last follow-up visit. WORMS and MOCART revealed cartilage repair in SVF-treated knees.
Kim et al., 2014[41]	Cohort study	49 pts (50 ankles)	Osteochondral lesion talus	Bone marrow stimulation + SVF (24) or bone marrow stimulation alone (26)	3.94 mil. cells	The mean VAS, AOFAS, Tegner, and MOCART scores improved significantly in the MSC group compared with the conventional group. Significant correlations of the MOCART score with clinical outcomes were found in both groups.
Nguyen et al., 2016[46]	Prospective cohort study	30 pts	OA K-L III or IV	Microfracture + SVF + PRP or microfracture alone	5 ml, 10 mil. SVF cells/ml	Significantly reduced pain and improved WOMAC, Lysholm, and VAS scores compared with the placebo group maintained for at least 18 mos.

AE, adverse event; ASES, The American Shoulder and Elbow Surgeons Shoulder Score; dGEMRIC, delayed gadolinium-enhanced MRI of cartilage; FXN, function score; GAG, glycosaminoglycans; IKDC, International Knee Documentation; K-L, Kellgren-Lawrence score; KSS, Knee Society Score; LEAS, Levels of Emotional Awareness Scale; mil., million; MOCART, Magnetic Resonance Imaging Osteoarthritis Knee Score; NPRS, Numeric Pain Rating Score; pts, patients; SVF, stromal vascular fraction; WORMS, Whole-Organ Magnetic Resonance Imaging Score.

- SVF injected “into the cartilage lesion surface” at the time of arthroscopy after chondroplasty of unstable cartilage
- Control knee received HA
- Standard PROs, MRI at 6 and 12 months

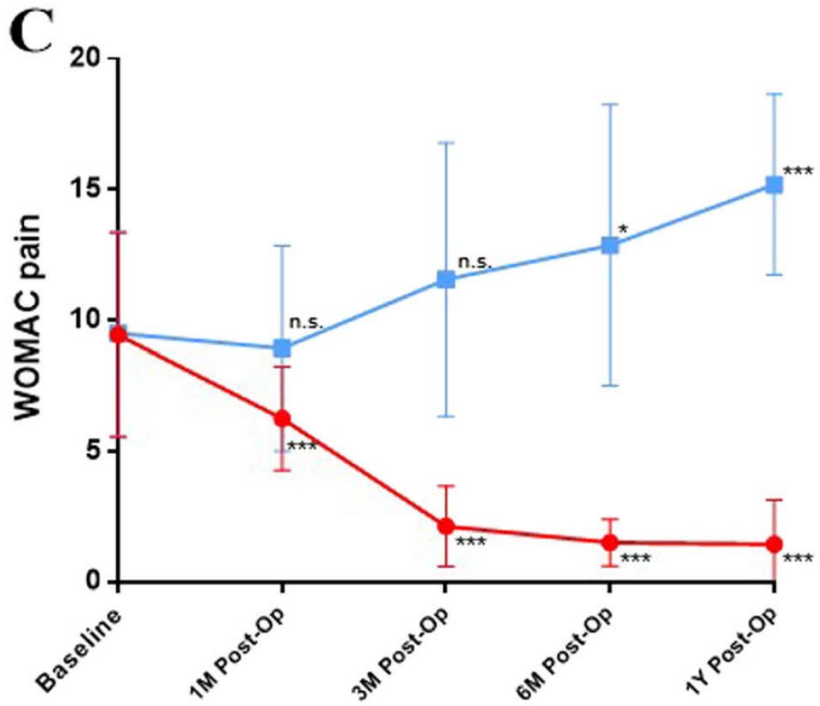


Fig. 2 Changes of VAS, WOMAC score, and knee ROM in two groups during 12-months follow-up. Values in graphs are expressed as mean ± SD in vertical bars, $^{**}P < 0.01$, $^{***}P < 0.001$, ns, non-significant ($P >$

Variables	Maximum score	Group test, *n* (%)		Group control, *n* (%)	
		6 months	12 months	6 months	12 months
1. Degree of defect repair and filling of the defect					
Complete	20	2 (12.50)	5 (31.25)	0 (0)	0 (0)
Hypertrophy	15	5 (31.25)	6 (37.50)	1 (6.25)	1 (6.25)
Incomplete					
> 50% of the adjacent cartilage	10	4 (25.00)	2 (12.50)	2 (12.50)	2 (12.50)
< 50% of the adjacent cartilage	5	3 (18.75)	2 (12.50)	4 (25.00)	3 (18.75)
Subchondral bone exposed	0	2 (12.50)	1 (6.25)	9 (56.25)	10 (62.50)
5. Signal intensity of repair tissue					
Normal (identical to adjacent cartilage)	30	3 (18.75)	5 (31.25)	1 (6.25)	1 (6.25)
Nearly normal (slight areas of signal alteration)	15	8 (50.00)	8 (50.00)	2 (12.50)	3 (18.75)
Abnormal (large areas of signal alteration)	0	5 (31.25)	3 (18.75)	13 (81.25)	12 (75.00)

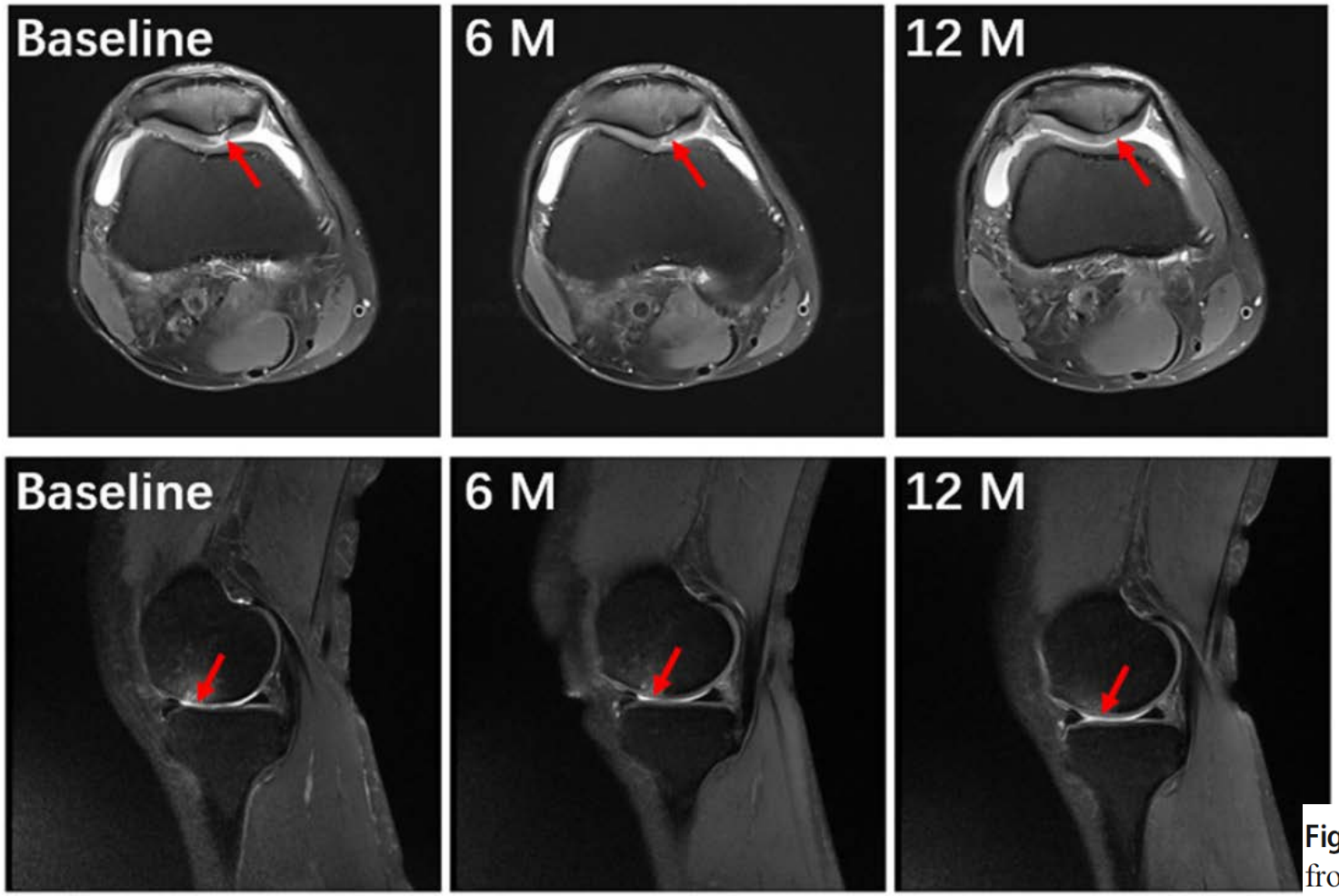


Fig. 3 Magnetic resonance imaging scans of three SVF-treated knees from baseline to 6 and 12-months follow-up showed complete repair and filling of the defects, as well as good integration with the adjacent cartilage and underlying bone in the coronal, transverse and sagittal planes (red arrows)

Intra-Articular Injection of Autologous Adipose Tissue-Derived Mesenchymal Stem Cells for the Treatment of Knee Osteoarthritis: A Phase IIb, Randomized, Placebo-Controlled Clinical Trial

Prospective double-blinded RCT

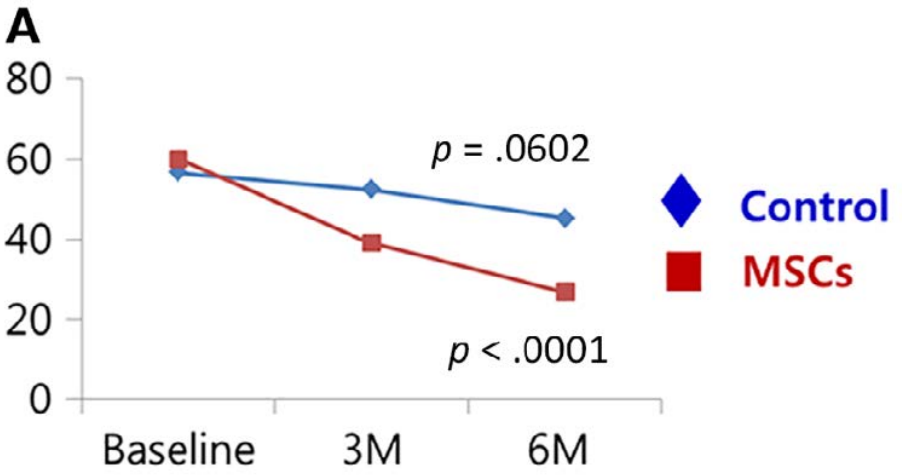
- AD-MSCs were administered for 12 patients (normal saline control)
- Primary outcome measure was the WOMAC
- Change of cartilage defect after injection was evaluated MRI

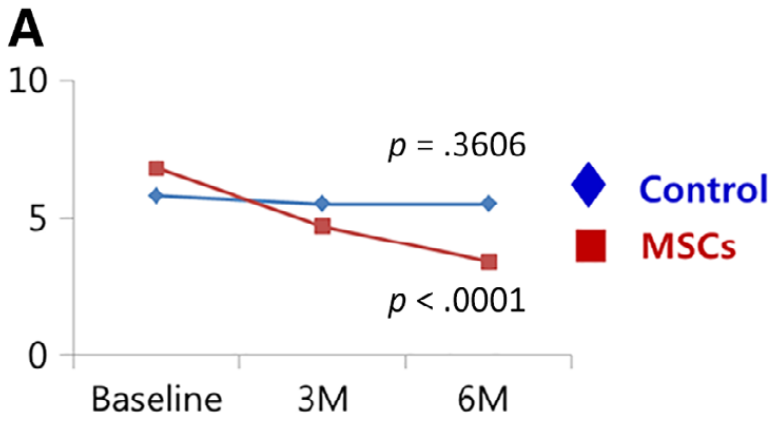
Results:

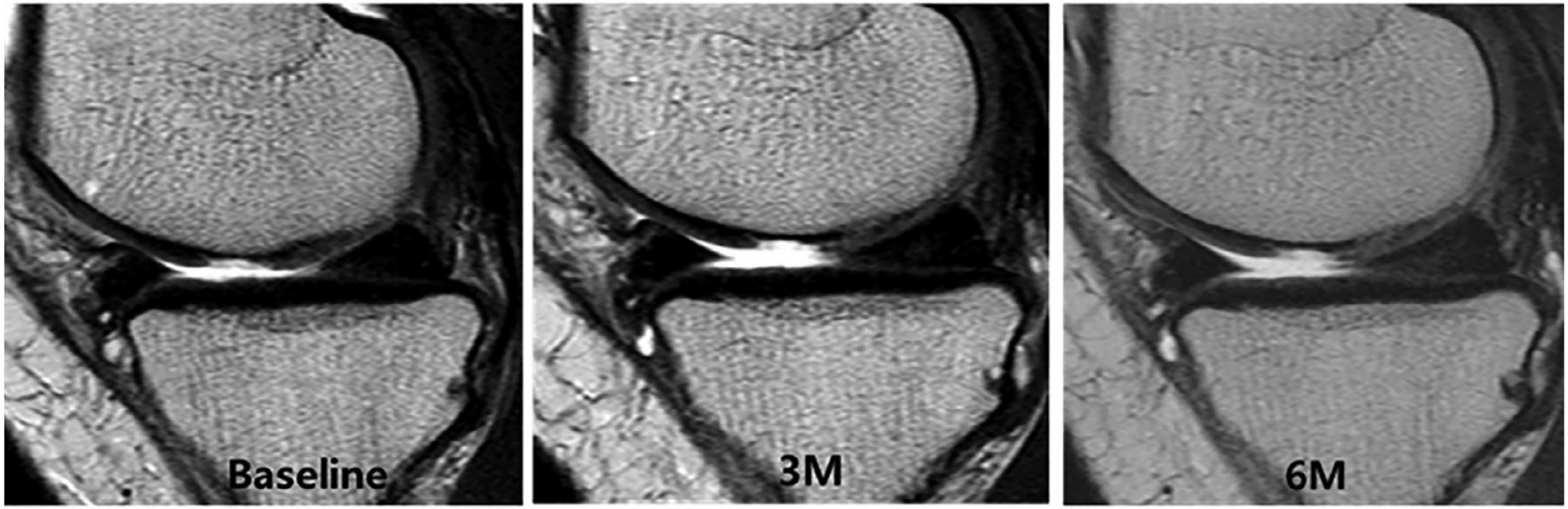
- Single injection of AD-MSCs led to a significant improvement in WOMAC score at 6 months
- MRI showed no significant change of cartilage defect at 6 months in MSC group
  - defect in the control group was larger

Characteristics	MSC group	Control group
Age, years	62.2 ± 6.5	63.2 ± 4.2
Gender, *n* (%)		
Male	3 (25)	3 (25)
Female	9 (75)	9 (75)
Height, cm	159.4 ± 7.2	159.8 ± 7.0
Weight, kg	66.5 ± 11.1	65.7 ± 12.4
Body-mass index	25.3 ± 4.9	25.4 ± 3.0
Kellgren-Lawrence grade, *n* (%)		
Grade 2	6 (50)	5 (41.7)
Grade 3	6 (50)	6 (50)
Grade 4	—	1 (8.3)
Mechanical axis, °	Varus 1.4° ± 5.7°	Varus 0.4° ± 3.6°
Baseline WOMAC score	60.0 ± 17.0	56.4 ± 16.3
Cartilage defect, mm^2[a]	312.4 ± 271.0	389.9 ± 273.0

[a]Cartilage defect means the defect in the femoral condyle of each participant.
Abbreviations: —, no data; MSC, mesenchymal stem cell; WOMAC, Western Ontario and McMaster Universities Osteoarthritis index.







- Culture expanded cells for Focal cartilage lesions or mild to moderate OA
- Normal BMI, intact meniscus and ligaments, no mal-alignment
- No evidence of cartilage restoration

Mesenchymal progenitor cells

TABLE 3. Studies assessing mesenchymal stem cells

Author, Year	Study Type	No. Studies/ Patients	Condition	Treatment	Volume/Dose	Outcomes
Iijima et al., 2018[56]	Meta-analysis	35 studies	Knee OA	MSCs	X	Significant improvement in pain, function and cartilage quality. However, the evidence for these outcomes was considered low to very low.
Pas et al., 2017[57]	Systematic review	5 RCTs and 1 non-RCT study	Knee OA	MSCs	X	All RCTs showed benefits in patient-reported outcomes and on imaging studies compared with control at 24–48 mos. 2 trials reported better histological or arthroscopic evaluations.
Freitag et al., 2019[61]	RCT	30 pts	Knee OA	Autologous AMSC cultured (1 or 2 doses) vs standard of care treatment	100 mil. 1 or 2 injections, 3 ml of isotonic fluid	Significant pain and functional improvement at 12 mos. Radiological analysis using MOCART indicated modification of disease progression.
Lee et al., 2019[62]	RCT	12 pts	Knee OA	Autologous AMSC cultured	100 mil. cells, 3 ml	WOMAC score was significantly improved at 6 mos in the AMSC group but not in the control group. The defect was stable in AMSC group but increased in the control group.
Koh et al., 2015[70]	RCT	44 pts	Knee cartilage defect	Microfracture + AMSCs or microfracture alone	Cell-thrombin-fibrinogen solution	In AMSCs group, the defect was healed compared with microfracture alone. The mean KOOS pain and symptom subscores were greater at follow-up in AMSCs than in microfracture. Second-look arthroscopy showed some tissue repair that was not significant.

Lamo-Espinoza et al., 2016[63]	RCT	30 pts	Knee OA	HA or autolog. BMSCs (2 groups for 2 doses 10 M or 100 M)	10 or 100 mil, in 1.5 ml or 3 ml Ringers Lactate followed by 4 ml of HA	VAS decreased in all follow-ups and at 12 mos. WOMAC improved at 6 mos in lower dose and was maintained to 12 mos in higher dose. X-ray showed reduction in knee joint space in controls only. ROM improved at 12 mos in BMSCs group only.
Gupta et al., 2016[64]	RCT	60 pts	Knee OA	Allogeneic BMSCs (Stempeucel), 25 M, 50 M, 75 M, 150 M	25, 50, 75, 150 mil. cells, in 2 or 4 ml or PLASMA-LYTE	Improvement in 25-M-cell dose group in VAS, ICOAP, and WOMAC scores (not statistically significant). AEs predominant in 50, 75, and 150 M cells, WORMS did not reveal any difference from baseline
Vega et al., 2015[65]	RCT	30 pts	Knee OA	Allogeneic BMSCs	40 mil. cells in 8 ml	MSC-treated patients displayed significant improvement in algofunctional indices vs controls. Quantification of cartilage by T2 relaxation measurements showed cartilage quality improvements in MSC patients.
Vangsness et al., 2014[66]	RCT	55 pts	Knee OA and meniscal regeneration	Allogeneic BMSC cultured (2 doses vs sodium hyaluronate)	50 or 150 mil. cells in HA, human serum albumin and PlasmLyte, 5 ml total	Pain relief in VAS score and significant improvement in 50 M dose (24% increase) vs in 150 M (6% increase) in meniscal volume.
Wong et al., 2013[67]	RCT	56 pts	Knee OA and genu varum	Microfracture + BMSCs with HA or + HA only	14 mil. in 0.5–1 ml	Age-adjusted assessments showed improvement in Lysholm, Tegner, and IKDC scores in favor of BMSCs.
Noriega et al., 2017[68]	RCT	24 pts	Degenerative disc disease	Allogeneic BMSCs	25 mil. cells	Responders (40% of the cohort) displayed improvement in algofunctional scores vs controls. Pfirrmann improved in the MSC-treated patients and worsened in the controls.

AMSCs, adipose-derived mesenchymal stem cells; HA, hyaluronic acid; ICOAP, Measure of Intermittent and Constant Osteoarthritis Pain; M, million; mil., million; pts, patients; WORMS, Whole-Organ Magnetic Resonance Imaging Score.

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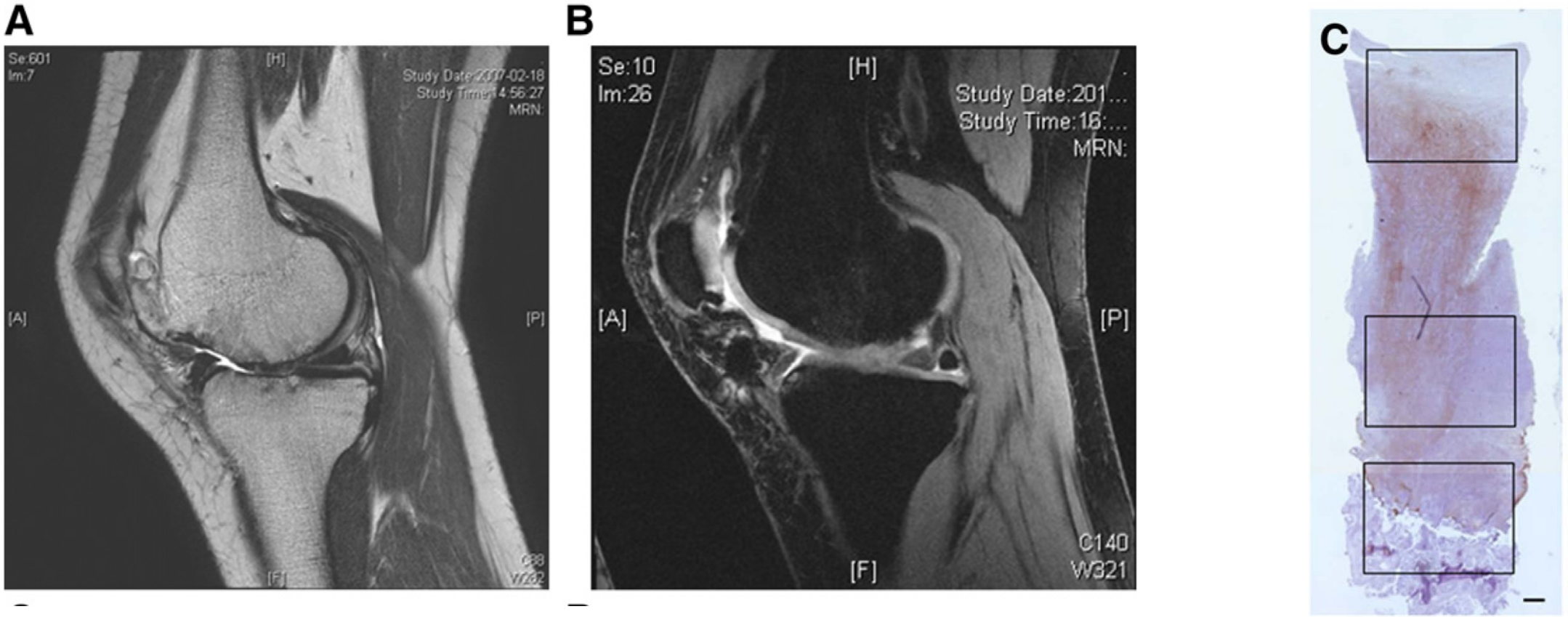
All show improvement from baseline in PROs

Concomitant Microfracture, No control group, small numbers

Amniotic Stem Cells

Cartilage Regeneration in Osteoarthritic Patients by a Composite of Allogeneic Umbilical Cord Blood-Derived Mesenchymal Stem Cells and Hyaluronate Hydrogel: Results from a Clinical Trial for Safety and Proof-of-Concept with 7 Years of Extended Follow-Up

- 7 patients with KL grade 3 OA and ICRS grade 4 cartilage defects
- Culture-expanded allogeneic hUCB-MSCs and hyaluronic acid hydrogel [Cartistem]
  - Injected into microfracture holes at time of arthroscopy
- The primary outcome was ICRS cartilage repair assessed by arthroscopy at 12 weeks.
  - IKDC, MRI, and histology



- Maturing repair tissue was observed at the 12-week arthroscopic evaluation.
- Clinical outcomes were stable over 7 years
- The histological findings at 1 year showed hyaline-like cartilage.
- MRI at 3 years showed persistence of the regenerated cartilage.

- Background
- Types of biologic therapies
- Current Research
- **Controversial issues**
- Summary

The Cost Variability of Orthobiologics

Amit Mukesh Momaya, MD,*† Andrew Sullivan McGee, BA,† Alexander R. Dombrowsky, BSc,†
Alan Joshua Wild, BSc,‡ Naqeeb M. Faroqui, BSc,§ Raymond P. Waldrop, BSc,† Jun Kit He, BSc,†
Eugene W. Brabston, MD,† and Brent Andrew Ponce, MD†

- 1345 Orthopedic sports medicine practices across the United States
- Phone call inquiring into the availability of PRP or SC knee injections and associated costs.

Table 1. Pricing statistics of platelet-rich plasma injections and stem cell injections

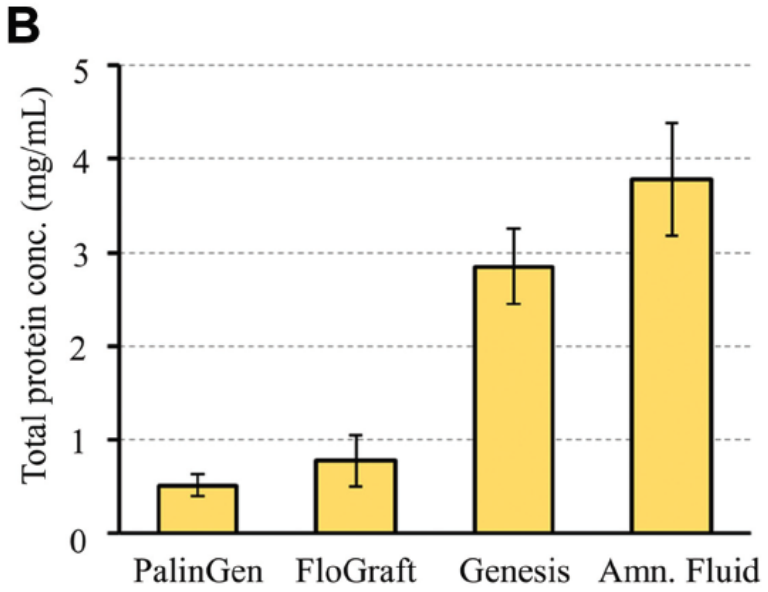
Cost	Platelet-Rich Plasma, n = 818	Stem Cell, n = 288
Mean ± SD, $	707 ± 388	2728 ± 1584
Median, $	630	2500
Highest, $	4973	12,000
Lowest, $	175	300

Are Amniotic Fluid Products Stem Cell Therapies?

A Study of Amniotic Fluid Preparations for Mesenchymal Stem Cells With Bone Marrow Comparison

Alberto J. Panero,*† DO, Alan M. Hirahara,† MD, FRCSC, Wyatt J. Andersen,† ATC, Joshua Rothenberg,‡ DO, and Fernando Fierro,§ PhD
Investigation performed at the University of California, Davis, Sacramento, California, USA

- 3 commercially available amniotic fluid products
- No viable MSC
- All nucleated cells were non-viable



FDA Regulation

- Biologic use in the clinical setting is dependent on FDA Approval
  - Regulated solely under section 361 of the Public Health Service Act and 21 CFR Part 1271

- Criteria include
  - Minimal manipulation
  - Intended for homologous use only
  - Not combined with another agent
  - Not expected to have any systemic effect
  - No reproductive use.

FDA Regulation

- All biologics prepared with more than minimum manipulation are considered drugs.
  - FDA approval for IND license is required

- Currently, only use of autologous PRP, MF, and BMAC may be considered as manufactured under the minimal manipulation definition.
  - Amniotic fluid or tissue does not meet the homologous use criteria

- Culture-expanded or further modified biologics are considered drugs and have to undergo the FDA approval to be used clinically.

FDA NEWS RELEASE

FDA seeks permanent injunctions against two stem cell clinics

Actions part of a comprehensive approach to the oversight of regenerative medicine products

- Background
- Types of biologic therapies
- Current Research
- Controversial issues
- **Summary**

Where are we in 2023

- “Despite positive and satisfactory results in numerous clinical trials, the complexity of MSC metabolism and related therapeutic effects as well as the weakness of most of the studies do not allow drawing definitive conclusions about the superiority of one tissue source over another, as well as about the best cell dose and the long-term durability of the effects of these procedures.”

What do I do in my practice

- I **do not** routinely using biologic therapies for joint preservation
- I **do** routinely refer patients to my non-operative sports med partner for PRP
  - Failed HA or insurance doesn't cover visco
- I **recommend against** other biologic therapies (MSC, amniotic fluid) due to high cost and minimal supportive data
- I **would consider** revisiting other injectable therapies if new data becomes available

Summary

- Biologic therapies are promising but much work needs to be done
- As currently used in the US, MPC do not restore cartilage
  - Likely need targeted therapy and a scaffold
- If you offer biologic therapies, please know current FDA regulations
- Don’t mislead or over-promise patients outcomes that haven’t been proven with high level research.

Thank you!