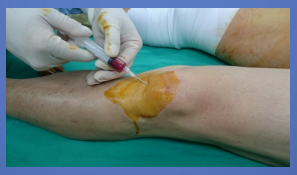
Is Platelet-Rich Plasma the Better Intra-articular Injection Choice for the Treatment of Knee Osteoarthritis?

A Prospective, Triple-Blind, Randomized, Placebo-controlled Trial



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Disclosure

- None pertinent to this study

Knee Osteoarthritis

- Prevalence: >20% in people >45 y/o; 37.4% in people ≧60 y/o (Lawrence et al. 2008; Center for Disease Control and Prevention. Osteoarthritis. Accessed Nov. 17, 2013))
- 2nd most common cause of work performance loss after low back pain (Stewart et al. 2003)
- Need for knee arthroplasty would rise >6 times by 2030 (De La Mata et al. 2013)

Conservative Treatment

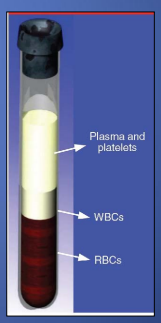
- Behavioral modification
- Oral medication (NSAIDs, Tramadol; Glucosamine?)
- Intra-articular injection
  - Steroids
    - Short-lasting effect (up to one month) (Cochrance Review 2006)
    - Systematic adverse effects
    - Joint cartilage destruction (Kon et al. 2012)
    - AAOS guideline recommendation: Inconclusive
  - Calcium gluconate/sodium bicarbonate (Garcia-Padilla et al. 2015)
  - Hyaluronic acid
  - Platelet-rich plasma (PRP) ?

Hyaluronic Acid (HA)

- Conflicting results on efficacy
  - Meta-analysis (89 trials, 12,667 pts): **No** clinically important benefits (Rutjes et al. *Ann Intern Med* 2012)
  - Meta-analysis (29 RCT, 4,866 pts): HA safe and effective for knee OA (Strand et al. *J Pain Res* 2015)
- Financial conflict of intertest: 63% industry funded studies (Printz et al. *J Arthroplasty* 2013)
- 2013 AAOS guideline: Strongly ***NOT*** recommended

Platelet-Rich Plasma

- " A sample of autologous blood with concentrations of platelets above baseline values." (Hall et al. ***JAAOS*** 2009)



PRP FOR OSTEOARTHRITIS ?

PRP FOR OA KNEE

Randomized-controlled trials in literatures

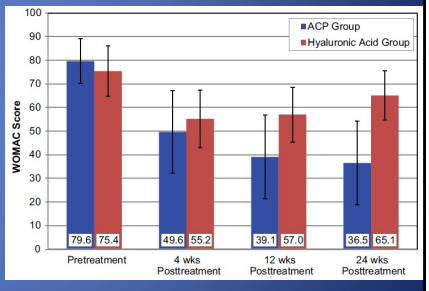
The American Journal of Sports Medicine

Comparison Between Hyaluronic Acid and Platelet-Rich Plasma, Intra-articular Infiltration in the Treatment of Gonarthrosis

Fabio Cerza, Stefano Carnì, Alessandro Carcangiu, Igino Di Vavo, Valerio Schiavilla, Andrea Pecora, Giuseppe De Biasi and Michele Ciuffreda

Am J Sports Med 2012 40: 2822 originally published online October 25, 2012
DOI: 10.1177/0363546512461902

- RCT (Jadad quality 2)
- 60 PRP (ACP) vs. 60 HA
  - 4 weekly injections
- F/U: 1, 3, 6 months
- WOMAC:
  - PRP > HA ($p < 0.001$)
  - PRP results not influenced by OA stage



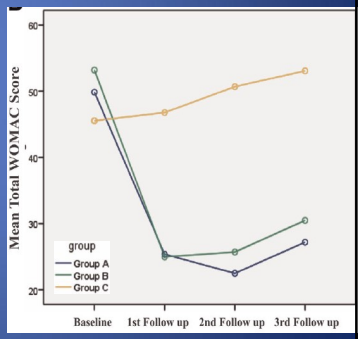
The American Journal of Sports Medicine

Treatment With Platelet-Rich Plasma Is More Effective Than Placebo for Knee Osteoarthritis: A Prospective, Double-Blind, Randomized Trial

Sandeep Patel, Mandeep S. Dhillon, Sameer Aggarwal, Neelam Marwaha and Ashish Jain

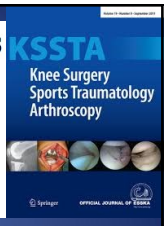
Am J Sports Med 2013 41: 356 originally published online January 8, 2013
DOI: 10.1177/0363546512471299

- Level-I RCT
- 156 knees (78 patients)
- 1 PRP (LP) vs. 2 PRP (3 wks apart) vs. NS
- F/U: 6 wks, 3, 6 months
- WOMAC:
  - 1PRP ≈ 2PRP > NS
  - PRP results deteriorates after 6 months
  - Grade I OA responded better than Grade II
  - No influence of age, sex, BMI



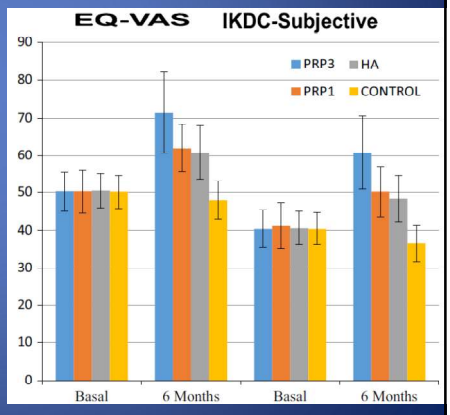
Multiple PRP injections are more effective than single injections and hyaluronic acid in knees with early osteoarthritis: a randomized, double-blind, placebo-controlled trial

Gökay Görmeli[1] · Cemile Ayşe Görmeli[2] · Baybars Ataoglu[3] · Cemil Çolak[4] · Okan Aslantürk[1] · Kadir Ertem[1]



Published online Aug. 2015

- Level I RCT, 162 patients
- PRP (3x) : PRP (1) : HA : N/S
- 3 weekly injections
- F/U: 6 months; IKDC, VAS
- Early OA pts:
  - PRP (3x) significantly better; PRP (1) ≈ HA
- Advanced OA:
  - No difference among groups



The American Journal of Sports Medicine

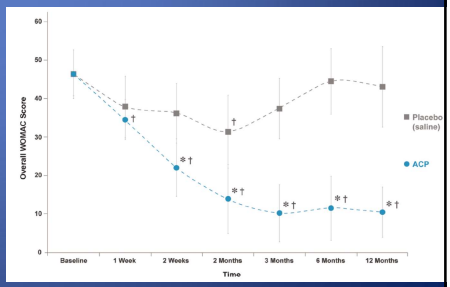
published on February 1, 2016

Intra-articular Autologous Conditioned Plasma Injections Provide Safe and Efficacious Treatment for Knee Osteoarthritis

An FDA-Sanctioned, Randomized, Double-blind, Placebo-controlled Clinical Trial

Patrick A. Smith,*† MD
Investigation performed at the Columbia Orthopaedic Group, Columbia, Missouri, USA

- Level I RCT
- LP-PRP (15) vs. N/S (15)
- 3 weekly injection (5-7 ml)
- F/U: 1 year
- ACP group: WOMAC score improved 78% compared to preop



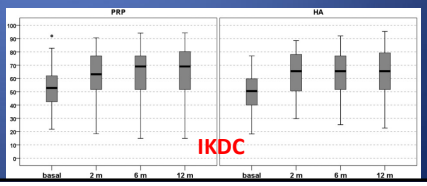
The American Journal of Sports Medicine

Platelet-Rich Plasma Intra-articular Knee Injections Show No Superiority Versus Viscosupplementation: A Randomized Controlled Trial

Giuseppe Filardo, Berardo Di Matteo, Alessandro Di Martino, Maria Letizia Merli, Annarita Cenacchi, PierMaria Fornasari, Maurilio Marcacci and Elizaveta Kon

Am J Sports Med 2015 43: 1575 originally published online May 7, 2015
DOI: 10.1177/0363546515582027

- 192 patients
- LR-PRP (2-spin) vs. HA (HMW)-- 3 weekly injections
- F/U: 2, 6, 12 months
- Both groups showed significant IKDC and VAS improvement
- **No** significant intergroup difference at any f/u periods



2013 AAOS Clinical Practice Guideline

- "*could not recommend for or against* PRP in the treatment of symptomatic knee osteoarthritis"

Kaohsiung Veterans General Hospital Randomized Control Trial

PRP *vs.* HA *vs.* N/S (placebo)

- **1st RCT on Chinese population**
- **1st RCT of RegenKit @ THT**
- **1st RCT of PRP *vs.* HA with a placebo group**
- **1st RCT using Generalized Estimating Equation (GEE) for statistical analysis**

Source of Funding

- Institutional research grant (VGHKS 103-075)
- Material supported:
  - ➢ PRP: RegenKit@ THT (Regen Lab SA, Switzerland)

  - ➢ HA: Hyruan Plus™ (LG Corporation, South Korea)

Patient Selection

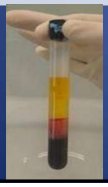
Inclusion Criteria	Exclusion Criteria
• Age > 20 • Unilateral or bilateral knee pain > 4 months • Diagnosis of OA by radiography (Ahlback stage I-III) • Possibility for observation during follow-up periods • No prior PRP injection • No HA injection within one year • No prior knee surgical procedure	• Ahlback OA stage 4 • Hb < 11 g/dL; Platelet count < 150,000/mm^3 • Major axial deviation (varus/valgus >5°) • Focal chondral or osteochondral lesion • Any concomitant symptomatic knee disorder (i.e ligamentous/ meniscal injury) • Systemic inflammatory arthropathy • Hematologic diseases • Severe cardiovascular disease • Neurological disorders • Active infection • Immunodepressed • Cancer history • Therapy with anticoagulants or antiaggregants • Use of NSAIDs 7 days prior to trial

Study Design

- **IRB (VGHKS14-CT2-15):** approved on 03/27/2014
- Single-center
- Randomized (computer randomization by Excel)
- 3 groups: PRP vs. HA vs. NS (placebo)
- Triple-blinded (patient, evaluator, data analyst)

Interventional Procedure

PRP	HA	NS
• 3 weekly injections • RegenLab Kit • Single-spin • LP-PRP (Mishra 3B) • 2ml/ injection	• 3 weekly injections • LG Hyruan Plus™ • MW≈2.5M Da • 2ml/ injection (10mg/ml)	• 3 weekly injections • 2ml/ injection



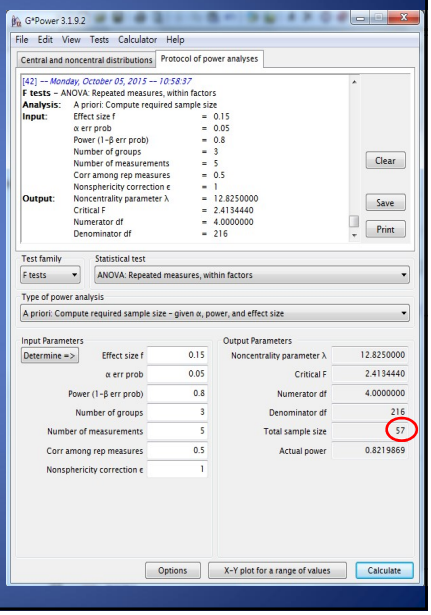
Injection Protocol

- Blood harvesting : 10ml before each injection regardless of grouping
- Single injector (KYL)
- Injection site: Anterolateral parapatellar
- No topical anesthesia

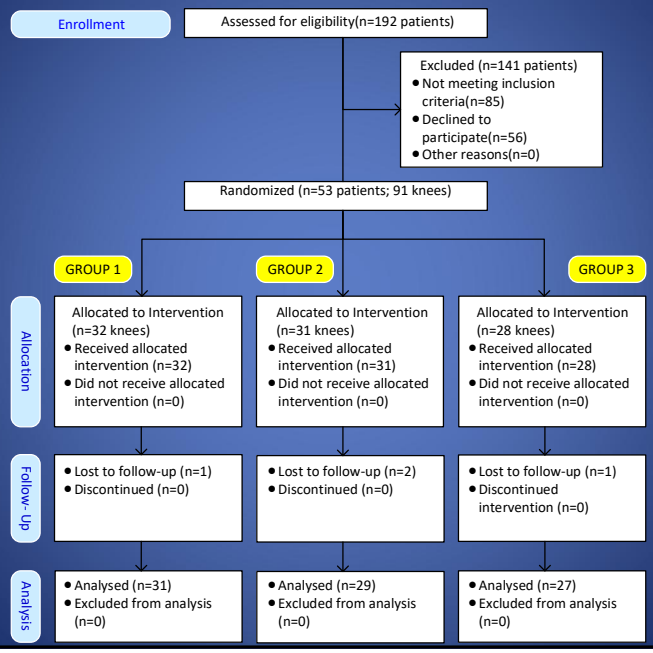
Sample Size and Power

G*Power 3.1.9.2

- α error probability = 0.05
- Power (1 – β error prob) = 0.8
- Effect size f = 0.15
- # groups = 3
- # measurement = 5
- Total sample size required = **57**



CONSORT FLOW DIAGRAM



Post-Injection Protocol

- Evaluated at: Baseline, 1, 2, 6, 12 months
- Functional outcomes (www.orthopaedicscores.com)
  - WOMAC (0 to 100)
  - IKDC subjective (0 to 100)

  } Higher score= Better result
- Evaluator (CCY) ≠ Injector (KYL)
- No NSAIDs and No additional IA injection allowed during the entire F/U period
- Acetaminophen discontinued 72 prior to each f/u date
- Resume routine ADL after each injection
- No additional rehabilitation prescribed

Statistical Analysis

- **ANOVA**: Evaluate **continuous variable** differences
- **χ^2 test**: Evaluate **categorical variable** differences
- **Generalized Estimating Equation (GEE) logistic model**: Multiple assessment of the within group and between groups differences of continuous and homoscedastic data
- **SAS 9.4** (SAS Institute Inc. NC, USA)

RESULTS

Baseline Characteristics of Patients

	Group1 (PRP)	Group2 (HA)	Group3 (NS)	p-value (<0.05)
53 patients, 91 knees	n=32	n=31	n=28	
Gender				0.775
Male (%)	9(29.03)	8(29.63)	10(37.04)	
Female (%)	22(70.97)	19(70.37)	17(62.96)	
Age(SD)	61.17(13.08)	62.53(9.9)	62.23(11.71)	0.8932
BMI (SD)	23.98(2.62)	26.26(2.99)	24.98(3.12)	0.0127
Ahlback stage				0.9448
I (%)	5(16.67)	6(20.69)	4(15.38)	
II (%)	16(53.33)	14(48.28)	12(46.15)	
III (%)	9(30)	9(31.03)	10(38.46)	
WOMAC (SD)	52.81(18.14)	52.67(18.06)	48.59(16.92)	0.6013
IKDC (SD)	35.71(13.77)	35.93(12.71)	33.3(10.52)	0.6838

Differences of **WOMAC** at different F/U time compared to baseline (Intragroup)

- PRP group $P < 0.0125$

WOMAC	1 mon	2 mon	6 mon	12 mon
Baseline	0.0001	0.0000	0.0052	0.0014

- HA group

WOMAC	1 mon	2 mon	6 mon	12 mon
Baseline	0.0000	0.0192	0.4421	0.1360

- NS group

WOMAC	1 mon	2 mon	6 mon	12 mon
Baseline	0.0015	0.0094	0.845	0.0872

Differences of **IKDC** at different F/U time compared to baseline (Intragroup)

- PRP group

P < 0.0125

IKDC	1 mon	2 mon	6 mon	12 mon
Baseline	0.0000	0.0000	0.0003	0.0003

- HA group

IKDC	1 mon	2 mon	6 mon	12 mon
Baseline	0.0001	0.0037	0.0357	1.0000

- NS group

IKDC	1 mon	2 mon	6 mon	12 mon
Baseline	0.0002	0.0433	0.3269	1.0000

PRP *vs.* **NS** (Intergroup)

Differences of **WOMAC** at different F/U time

F/U						
1 mon	**1.9537**	**2.8837**	**-3.6984**	**7.6057**	**0.68**	**0.4981**
2 mon	**8.7195**	**2.7548**	**3.3202**	**14.1189**	**3.17**	**0.0015**
6 mon	**7.9396**	**3.2801**	**1.5107**	**14.3684**	**2.42**	**0.0155**
12 mon	**11.9186**	**3.7407**	**4.5869**	**19.2504**	**3.19**	**0.0014**

P < 0.025

- PRP ≈ NS at F/U 1 mon
- PRP > NS at F/U 2 mon, 6 mon, 12 month

PRP *vs.* NS (Intergroup)

Differences of **IKDC** at different F/U time

F/U						
1 mon	2.3502	1.9844	-1.5391	6.2396	1.18	0.2363
2 mon	9.1034	2.3897	4.4196	13.7872	3.81	0.0001
6 mon	10.2821	2.7636	4.8655	15.6987	3.72	0.0002
12 mon	13.967	2.948	8.1891	19.7449	4.74	<.0001

$P < 0.025$

- PRP ≈ NS at F/U 1 mon
- PRP > NS at F/U 2 mon, 6 mon, 12 month

HA *vs.* NS (Intergroup)

Differences of **WOMAC** at different F/U time

F/U						
1 mon	1.9862	2.7774	-3.4573	7.4297	0.72	0.4745
2 mon	2.7201	2.6655	-2.5042	7.9445	1.02	0.3075
6 mon	-2.2398	2.707	-7.5454	3.0657	-0.83	0.408
12 mon	-3.3738	3.1874	-9.621	2.8734	-1.06	0.2898

$P < 0.05$

- HA ≈ NS at all F/U times

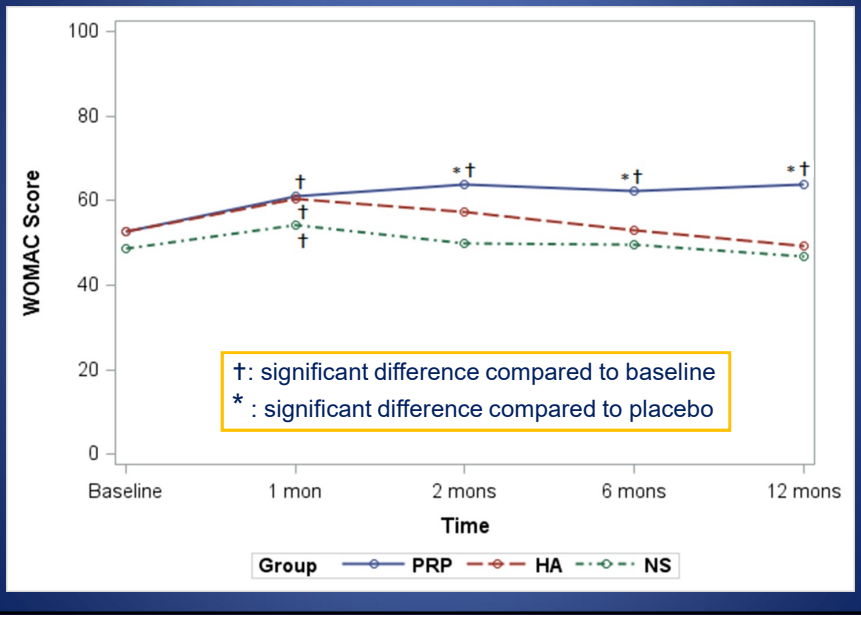
HA *vs.* NS (Intergroup)
Differences of **IKDC** at different F/U time

F/U						
1 mon	2.0859	2.2789	-2.3807	6.5526	0.92	0.36
2 mon	4.109	2.66	-1.1044	9.3225	1.54	0.1224
6 mon	3.0972	2.5702	-1.9403	8.1346	1.21	0.2282
12 mon	2.4752	2.9094	-3.2271	8.1774	0.85	0.3949

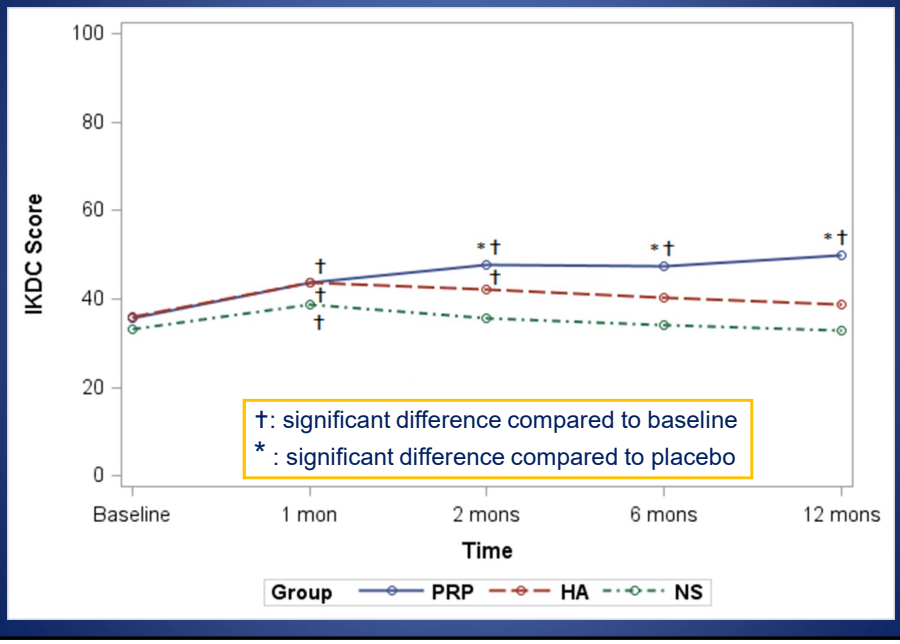
$P < 0.05$

➢ HA ≈ NS at all F/U times

WOMAC



IKDC



Other Influential Factors (WOMAC)

	Coef.	P>z	95% Conf.
Gender √	-8.3265	0.0135	-14.931
Age √	-0.4351	0.0044	-0.7346
Ahlback stage	1.372398	0.615	-3.976655
BMI	-0.7812	0.1595	-1.8698

Gender: female vs. male $P < 0.05$

Statistical analysis: GEE

Other Influential Factors (IKDC)

	Coef.	P>z	95% Conf.
Gender	-4.7086	0.0516	-9.4507
Age √	-0.3699	0.0009	-0.5885
Ahlback stage	-2.508315	0.207	-6.403627
BMI	-0.3686	0.3908	-1.2105

Gender: female vs. male $P < 0.05$

Statistical analysis: GEE

DISCUSSION

WOMAC

- Compare to baseline score (Intragroup):
  - PRP group: (+) Statistically significant improvement for 12 months; 21%
  - HA group, NS group: Significant improvement only for 1 month F/U
- Compare 3 groups (Intergroup):
  - F/U 1 mon: PRP ≈ HA ≈ NS
  - F/U 2 - 12 mon: PRP > HA ≈ NS (p <0.025)

IKDC

- Compare to baseline score (Intragroup):
  - PRP group: (+) Statistically significant for 12 months; 40%
  - HA group: (+) Significant improvement up to 2 mon
  - NS group: Significant improvement only at 1 month
- Compare 3 groups (Intergroup):
  - F/U 1 mon: PRP ≈ HA ≈ NS
  - F/U 2 - 12mon: PRP > HA ≈ NS (p <0.025)

Other Findings
(with statistics significance)

- Ahlback stage: No influence
- BMI: No influence
- Age: the Younger the better results
- Gender: Male had better results on WOMAC
- No adverse effect
  - only transient local discomfort lasting for hours
  - Unrelated to the type of injection

Strength of the Study

- RCT quality: Jadad score 5 (Jadad et al. *Control Clin Trials* 1996)
- Sufficient patients for adequate statistical power
- Blood drawn before each injection
  - Blinding
  - Avoid possible degranulation of platelets due to freezing/thawing (Blajchman *Transfus Clin Biol.* 2001)
- Limited loss to follow-up (2 patients/4 knees)
- Use of GEE for statistic analysis
- Although the tested materials were provided by the industry, the study was investigator initiated and driven

Limitation of the Study

- Inclusion of bilateral knee OA patients
  - But, this approach closely reflects regular clinical practice, validating our results to a larger clinical patient population
- No objective evaluation of the effects of treatment on the morphology of the cartilage
  - Image (MRI, X-ray)
  - Joint fluid (cellular/cytokines) analysis

Future Directions

- A large-scale multi-center RCT
- Optimal treatment protocol
  - preparation method
  - dose
  - numbers
  - interval
- PRP vs. PRP + HA (Chen et al. *Biomaterials* 2014)
- Image evaluation
- Post-injection cellular analysis of joint fluid

CONCLUSION

- PRP is safe and efficacious for treatment of OA knee, at least for one year
- Effect of HA subsided after 2 months
- The fact that outcome improvement lasted longer than HA and placebo…
  - PRP may have regenerative or disease-modifying effects on cartilage in the long run
- Hyaluronic acid injection is not more effective than a placebo (RCT by van der Weegen et al, *J Arthroplasty* 2015)

Thanks for Your Attention !!