Con il Patrocinio di

REGIONE PIEMONTE · CONSIGLIO REGIONALE DEL PIEMONTE · CITTÀ DI TORINO · UNIVERSITÀ DEGLI STUDI DI TORINO

APPROCCI INTERDISCIPLINARI IN REUMATOLOGIA

6ª Edizione

GERIATRIA E MALATTIE REUMATICHE

TRATTAMENTO INFILTRATIVO NELL'OSTEOARTROSI

Simone Parisi

AOU Città della Salute e della Scienza di Torino - SC Reumatologia

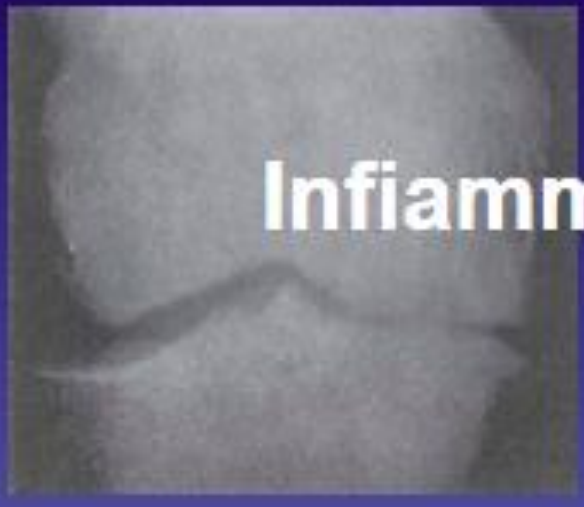
Torino, 12-13 ottobre 2018

AZIENDA OSPEDALIERO-UNIVERSITARIA Città della Salute e della Scienza di Torino

S.C. Reumatologia AO Città della Salute e della Scienza di Torino

Gli obiettivi della cura dell'artrosi

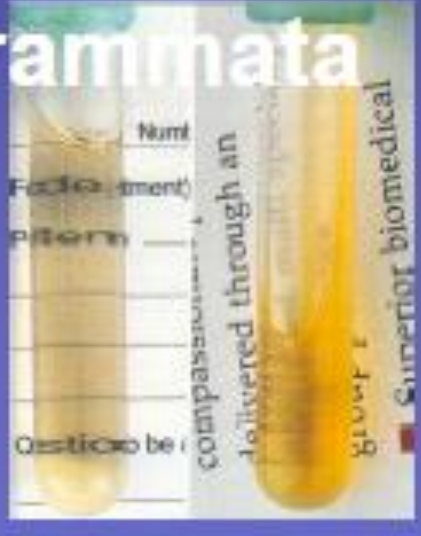
Patogenesi dell'OA



Infiammazione della Membrana Sinoviale

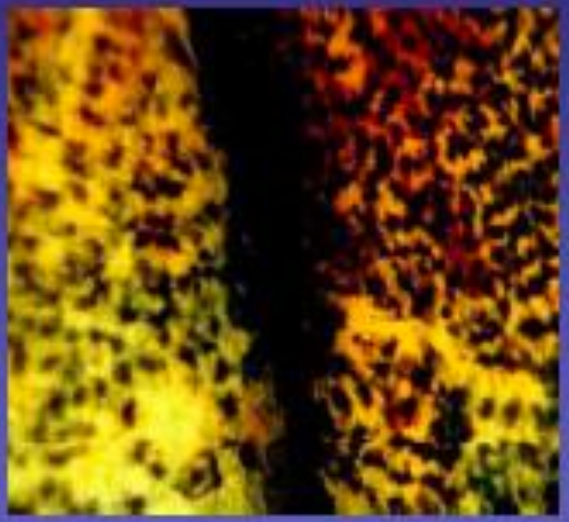
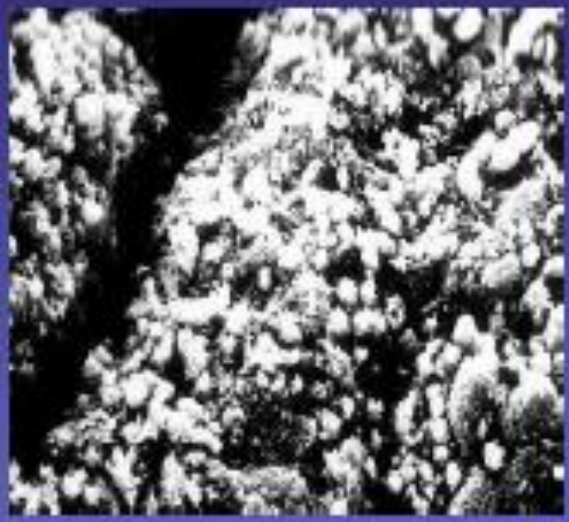
+

Apoptosi: Morte Cellulare Programmata



La membrana sinoviale

viene invasa da cellule infiammatorie

che si stratificano su tutta la superficie sinoviale

IMMUNOPATOGENESI

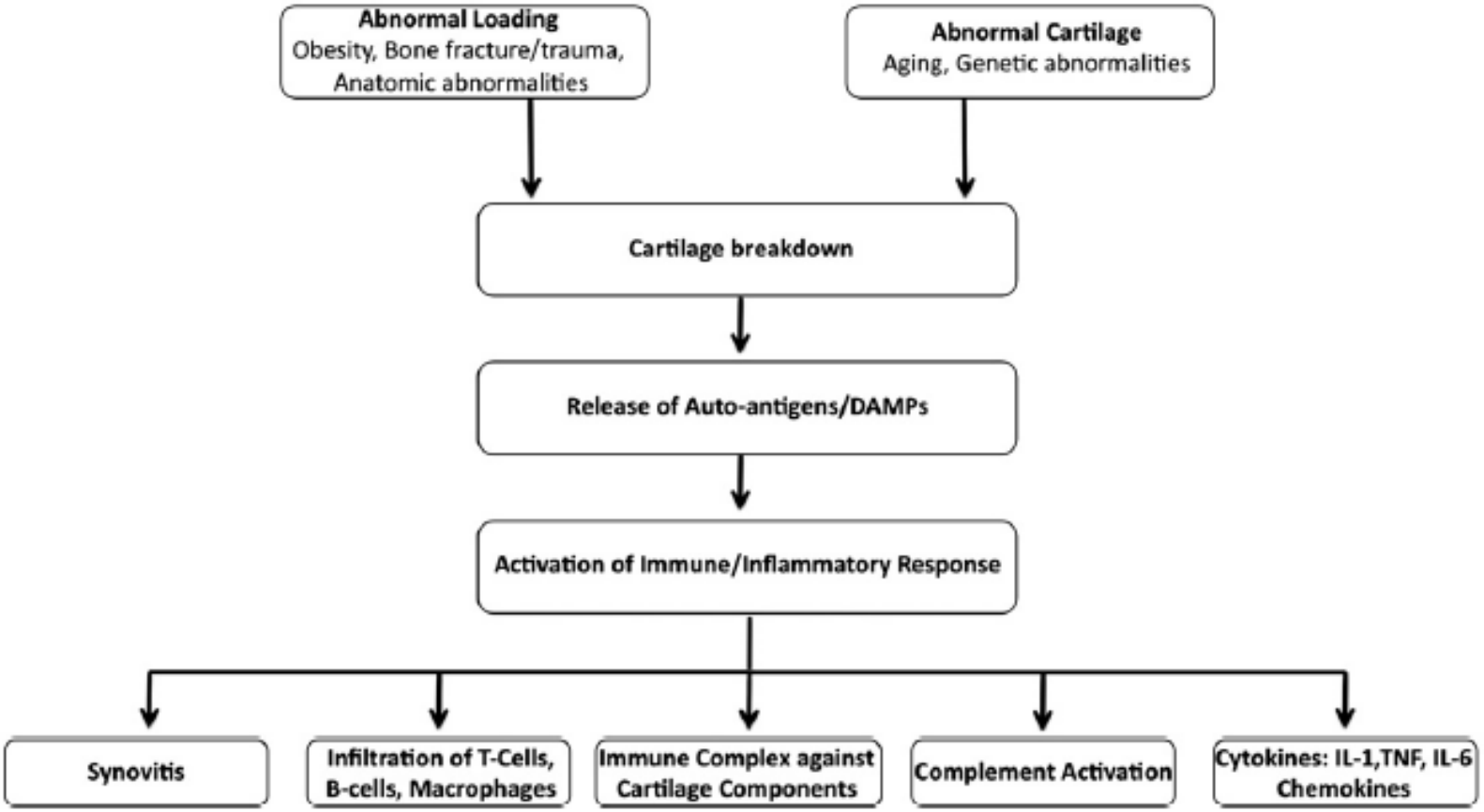


Figure 1 Schematic representation of immunopathogenesis of OA. Several genetic, metabolic as well as environmental factors lead to the damage of the cartilage resulting in the release of cartilage specific autoantigens, which in turn activate the immune/ inflammatory response. There is increased infiltration of T-cells, B-cells and macrophages in the joint tissues. These immune cells along with other cells of the joint tissue get activated and release several molecules such as cytokines, chemokines and other cartilage degrading factors such as MMPs and PGE_2 resulting in further degradation in the cartilage. DAMPs: damage-associated molecular patterns.

Contents lists available at ScienceDirect

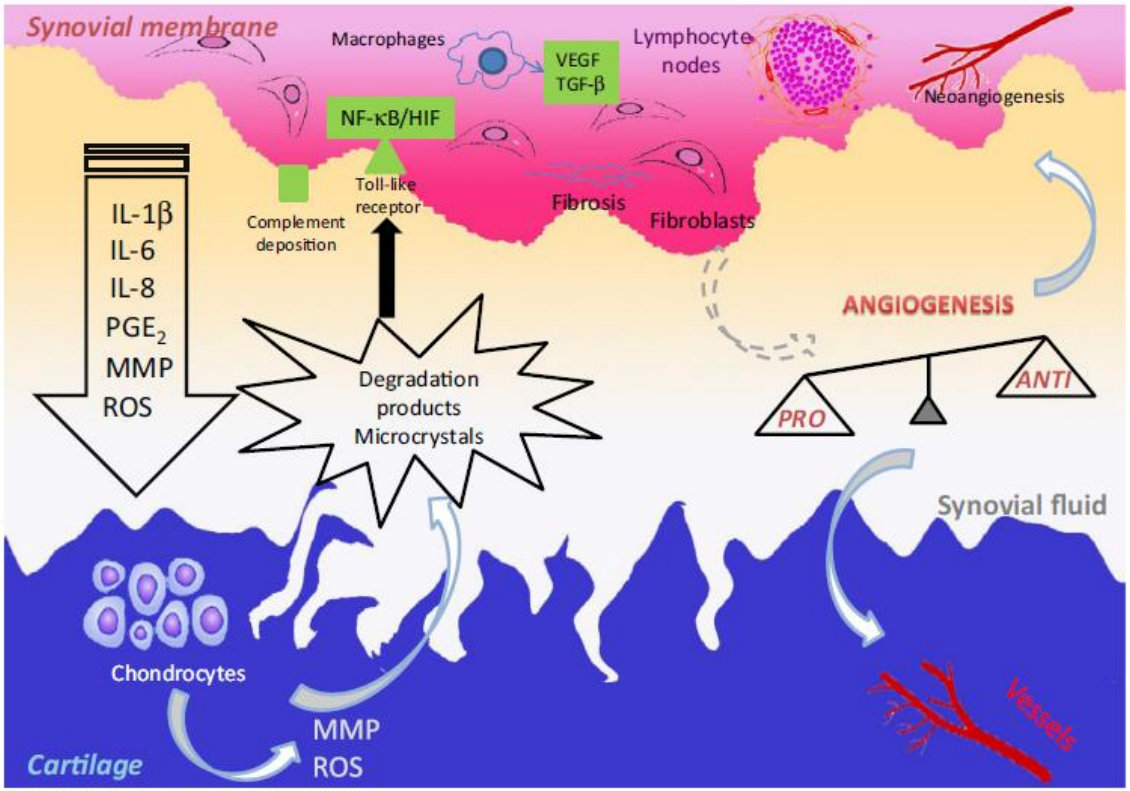
Seminars in Arthritis and Rheumatism

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

Importance of synovitis in osteoarthritis: Evidence for the use of glycosaminoglycans against synovial inflammation

Yves Henrotin, PhD[a,*], Cécile Lambert, PhD[a], Pascal Richette, MD, PhD[b,c]

[a] Bone and Cartilage Research Unit, Institute of Pathology, CHU Sart-Tilman, 4000 Liège, Belgium
[b] AP-HP, Hôpital Lariboisière, Pôle appareil locomoteur, fédération de rhumatologie, F-75010, Paris, France; Univ. Paris Diderot, Sorbonne Paris Cité, F-75205, Paris, France
[c] Sorbonne Paris Cité, University Paris Diderot, Paris, France



Effectiveness of intra-articular therapies in osteoarthritis: a literature review

Peter Wehling, Christopher Evans, Jana Wehling and William Maixner

Ther Adv Musculoskel Dis
2017, Vol. 9(8) 183–196
DOI: 10.1177/1759720X17712695

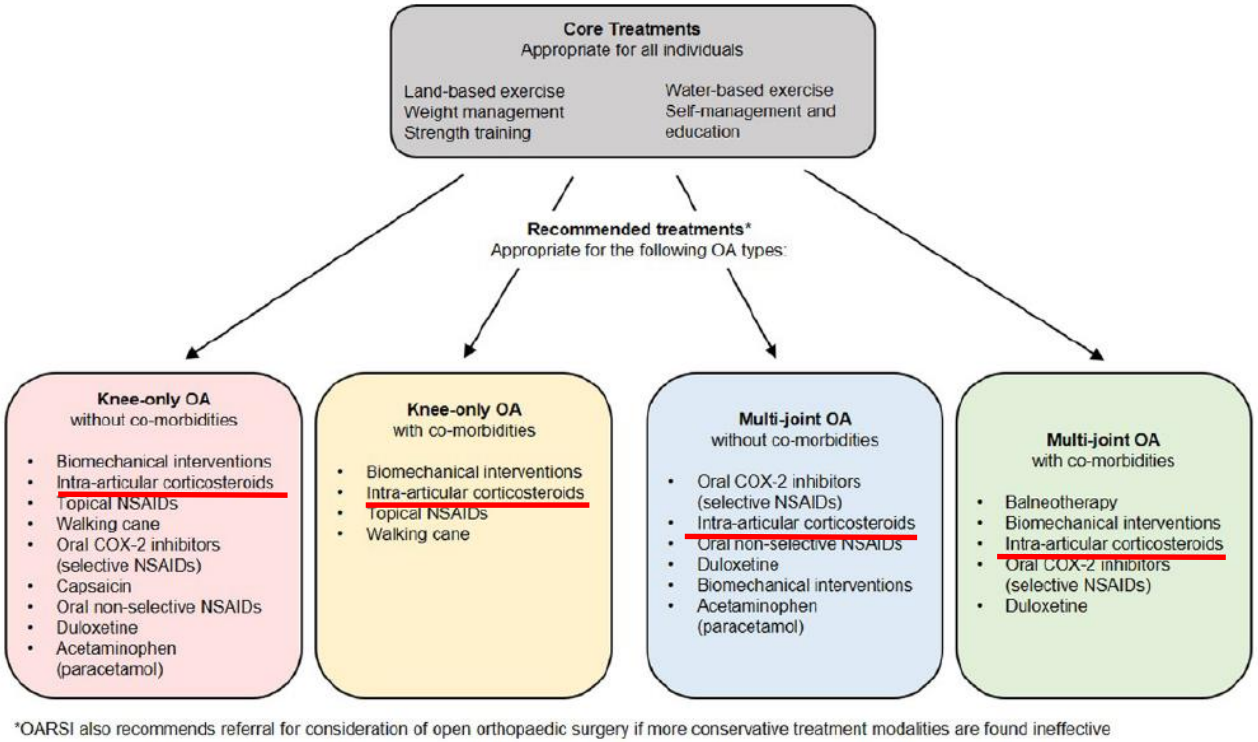


Figure 1. OARSI guidelines for the nonsurgical management of knee OA.
Adapted from McAlindon and colleagues.[10]
NSAID, nonsteroidal anti-inflammatory drug; OARSI, Osteoarthritis Research Society International; OA, osteoarthritis.

Table 1. Summary of IA therapies.

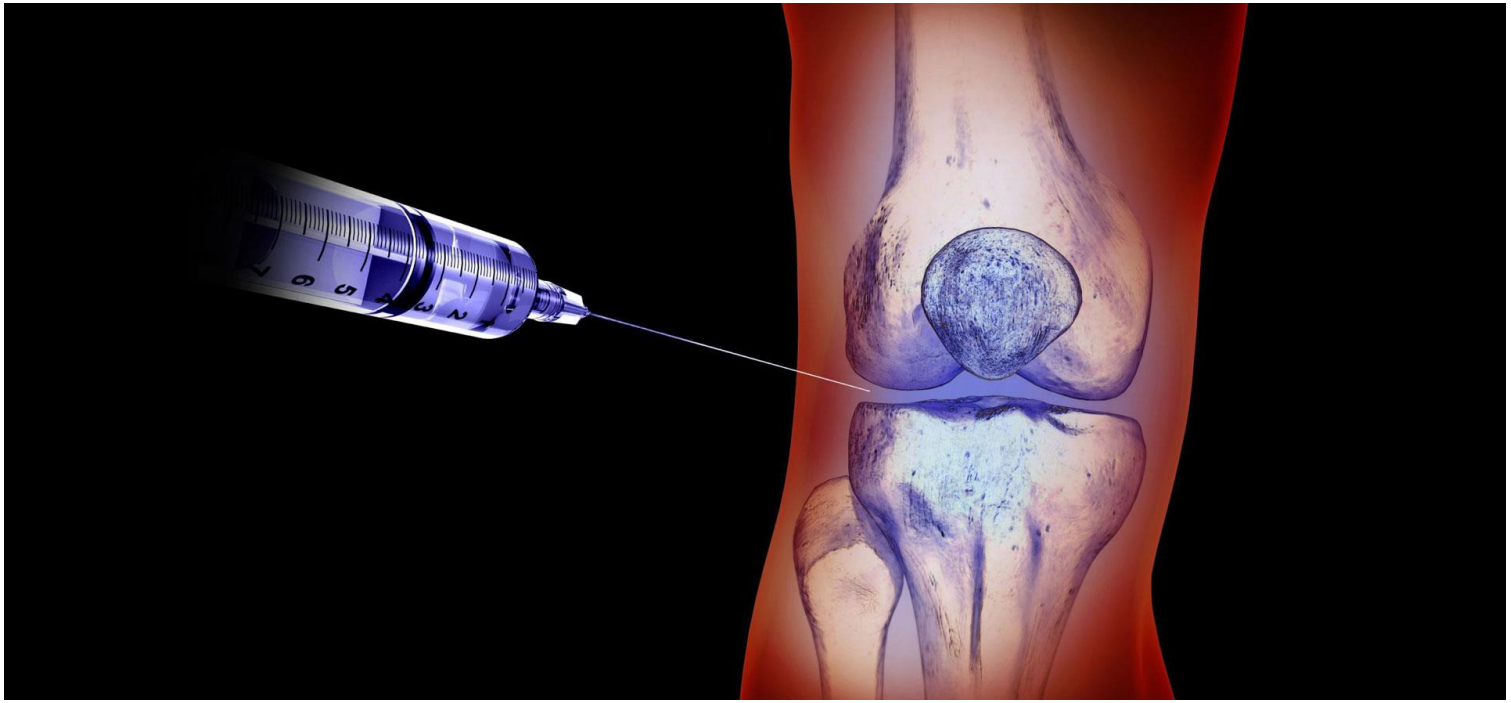
	Corticosteroids	HA	Platelet-rich plasma	Autologous conditioned serum	Mesenchymal stem cells
Components	Glucocorticoid (usually triamcinolone), in suspension	Hyaluronic acid or its sodium salt (sodium hyaluronate)	Plasma containing cells and coagulation factors, plus additives [anticoagulants, fibrinogen, activator ($Ca^{2}+$)]. Cell concentration varies depending on manufacturers' processing recommendations	Cell-free serum without platelets, white or red blood cells or additives. Standardized manufacturing process	Suspension of multipotent adult stem cells
Mechanism of action	Anti-inflammatory agent	Lubricating component of synovial fluid	Growth factor release, including TGF-β, PDGF, IGF, VEGFs, EGF and FGF-2	Elevated concentration of anti-inflammatory cytokines (including IL-1Ra, IL-4 and IL-10) and regenerative growth factors	Stem cell-secreted factors including cytokines and growth factors
Preparation and administration	Product injection directly into the joint	Product injection directly into the joint	Platelet enrichment in device from anticoagulated blood by centrifugation and elimination of superfluous plasma. Platelet yield is usually 50–75%. PRP may be activated with $Ca^{2}+$, and then injected directly (single injection). Sterile filtration not possible	Serum conditioning by incubation of whole blood in a pyrogen-free device at 37°C. Conditioning stimulates production of cytokines including IL-1Ra. Serum is separated by centrifugation and extracted/stored at –18°C for ≤7 months. Injection 3–6 times per visit, given twice a week for 3 weeks, 1–3 times, sterile filtration possible	MSCs can be isolated from several organs and tissues (e.g. bone marrow) and grown using various cell culture techniques
Efficacy	Evidence for short-term efficacy over placebo. Long-term benefits less well substantiated[11,22]	Incongruous literature regarding efficacy and safety: some indicating a good efficacy,[24] others suggesting HA provides little or no benefit over placebo.[25,26]	Most reviews provide evidence of clinical benefits,[27,28] some remain equivocal.[29]	Limited data due to less expanded use and nonconsideration in guidelines. Clinical studies indicate significant improvements over placebo and saline.[30]	Efficacy data are very limited, albeit encouraging.[31–37] Further studies are ongoing.
Safety	Prolonged exposure may adversely affect articular cartilage or be associated with chondrotoxicity	Incongruous literature, some meta-analyses concluding HA to have a low risk of harm,[26] others identifying concerning safety signals, albeit with unclear causal mechanisms.[25]	Perceived favorable safety profile due to autologous nature. Limited evidence available from long-term safety studies. Some evidence that PRP injections may lead to an increase in adverse events.[28,38]	Perceived favorable safety profile due to autologous nature. Limited data are available, but no serious side effects have been observed in published trials.[30,39]	Based on limited data available to date, IA MSC therapy appears to be relatively safe.[40,41]
Treatment recommendations	OARSI recommend corticosteroids, but recognize that other treatments may be more appropriate for long-term analgesia.[10]	OARSI do not recommend HA in multi-joint OA and cite uncertainty in the use of HA to treat knee OA.[10]	Not considered by OARSI in OA treatment recommendations	Not considered by OARSI in OA treatment recommendations	Not considered by OARSI in OA treatment recommendations

ACS, autologous conditioned serum; CS, corticosteroid; EGF, epidermal growth factor; FGF-2, basic fibroblast growth factor; HA, hyaluronic acid; IA, intra-articular; IGF, insulin-like growth factor; IL-1Ra, interleukin-1 receptor antagonist; IL-4, interleukin-4; IL-10, interleukin-10; MSC, mesenchymal stem cell; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International; PDGF, platelet-derived growth factor; PRP, platelet-rich plasma; TGF-β, transforming growth factor beta; VEGF, vascular endothelial growth factor.

TERAPIA INTRA-ARTICOLARE NELL' OA

- **TERAPIA INFILTRATIVA CON STEROIDI**

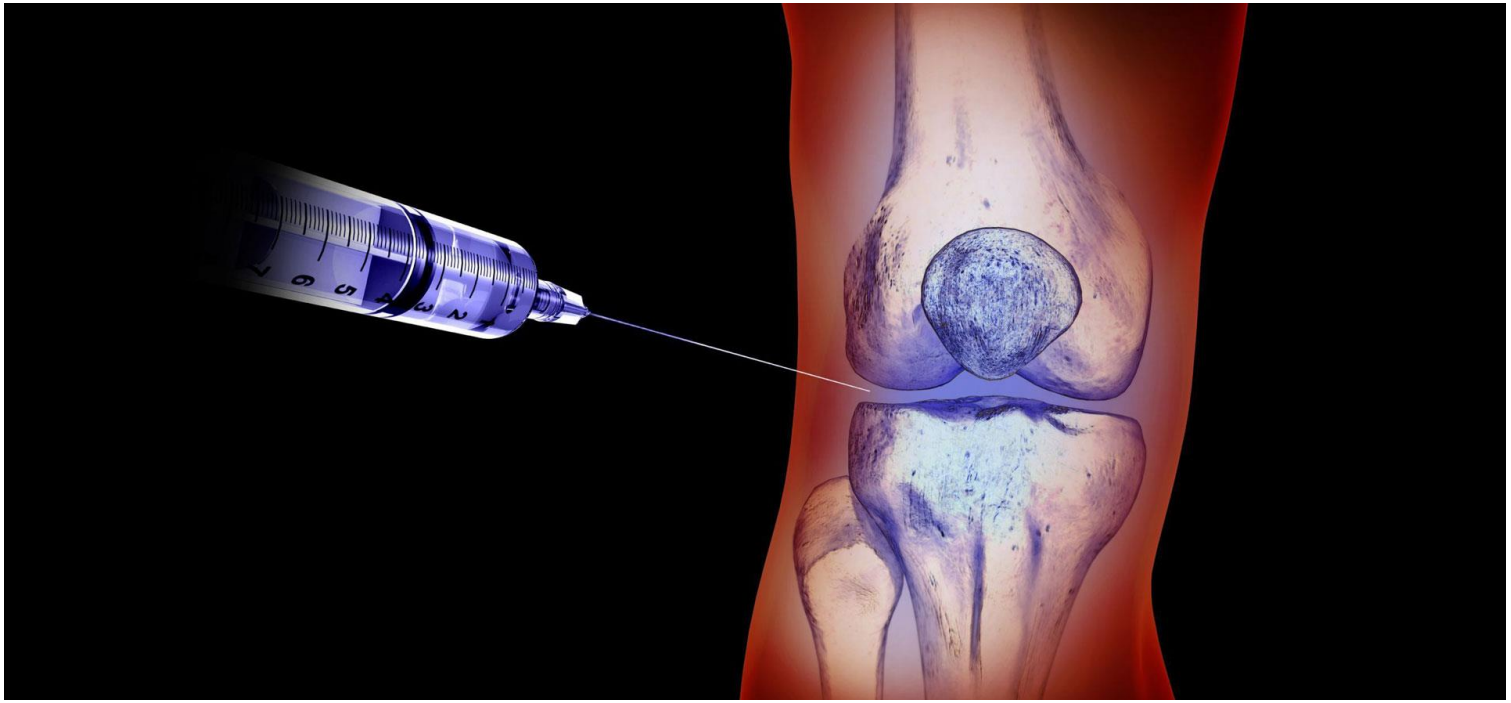
- **TERAPIA INFILTRATIVA CON ACIDO IALURONICO**



TERAPIA INTRA-ARTICOLARE NELL' OA

- **TERAPIA INFILTRATIVA CON STEROIDI**

- **TERAPIA INFILTRATIVA CON ACIDO IALURONICO**



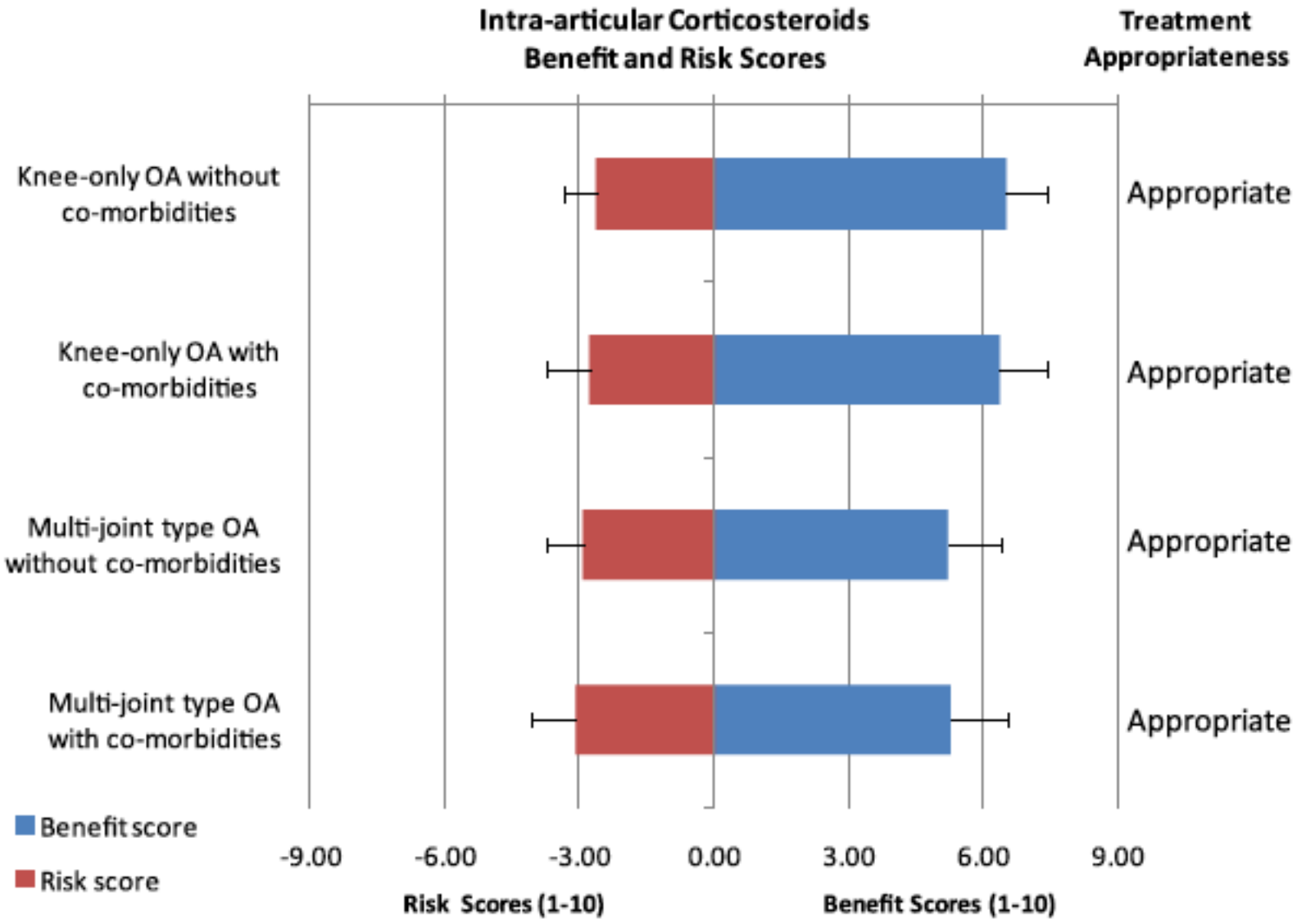
TERAPIA INFILTRATIVA CON STEROIDI

1. Utilizzata da circa 5 decadi. Levaeax and Quinn nel 1956 pubblicarono per primi l'efficacia di infiltrazioni con idrocortisone + procaina nell'OA dell'anca. Vasta letteratura a supporto dell'efficacia della terapia infiltrativa con steroidi in OA
2. Raccomandata dalle linee guida in particolare da ACR 2012 per ginocchio ed anca
3. Diversi studi riportano un tendenziale minor mantenimento dell'efficacia nel lungo termine (12 settimane)
4. Diversi studi sperimentali in vitro evidenziano come l'utilizzo di glucocorticoidi + anestetici possa avere effetto condrotossico.

Osteoarthritis and Cartilage

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

OARSI guidelines for the non-surgical management of knee osteoarthritis


Intra-articular Corticosteroids
Benefit and Risk Scores
Treatment Appropriateness
Knee-only OA without co-morbidities
Knee-only OA with co-morbidities
Multi-joint type OA without co-morbidities
Multi-joint type OA with co-morbidities
Appropriate
Appropriate
Appropriate
Appropriate
Benefit score
Risk score
-9.00
-6.00
-3.00
0.00
3.00
6.00
9.00
Risk Scores (1-10)
Benefit Scores (1-10)

Cochrane Library

Cochrane Database of Systematic Reviews

Intra-articular corticosteroid for knee osteoarthritis (Review)

Jüni P, Hari R, Rutjes AWS, Fischer R, Silletta MG, Reichenbach S, da Costa BR

Authors' conclusions

Whether there are clinically important benefits of intra-articular corticosteroids after one to six weeks remains unclear in view of the overall quality of the evidence, considerable heterogeneity between trials, and evidence of small-study effects. A single trial included in this review described adequate measures to minimise biases and did not find any benefit of intra-articular corticosteroids.

In this update of the systematic review and meta-analysis, we found most of the identified trials that compared intra-articular corticosteroids with sham or non-intervention control small and hampered by low methodological quality. An analysis of multiple time points suggested that effects decrease over time, and our analysis provided no evidence that an effect remains six months after a corticosteroid injection.

Figure 3. Forest plot of comparison: 1 Pain, outcome: 1.1 Pain - Main.

Study or Subgroup	Std. Mean Difference	SE	IA Corticosteroid Total	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Beyaz 2012	-0.68667	0.291396	25	25	3.8%	-0.69 [-1.26, -0.12]
Campos 2013	-0.4102612	0.1991779	52	51	4.8%	-0.41 [-0.80, -0.02]
Castro 2007	0.153865	0.25452	32	30	4.2%	0.15 [-0.34, 0.65]
Cederlof 1966	0.343675	0.443639	26	25	2.6%	0.34 [-0.53, 1.21]
Chao 2010	-0.8324666	0.2550403	34	33	4.2%	-0.83 [-1.33, -0.33]
Di Sante 2012	-1.269434	0.3481429	20	20	3.3%	-1.27 [-1.95, -0.59]
Dieppe 1980	-0.8378893	0.4273436	12	12	2.7%	-0.84 [-1.68, -0.00]
Friedman 1980	-0.06448	0.343092	17	17	3.3%	-0.06 [-0.74, 0.61]
Frías 2004	0	0.1396861	103	103	5.4%	0.00 [-0.27, 0.27]
Gaffney 1995	-0.0516039	0.2182551	42	42	4.6%	-0.05 [-0.48, 0.38]
Grecomoro 1992	0.2	0.3170589	20	20	3.6%	0.20 [-0.42, 0.82]
Henriksen 2015	-0.0392837	0.2000197	50	50	4.8%	-0.04 [-0.43, 0.35]
Jones 1996	-0.9257629	0.2721303	30	30	4.0%	-0.93 [-1.46, -0.39]
Lyons 2005	-0.566251	0.4570631	10	10	2.5%	-0.57 [-1.46, 0.33]
Miller 1958	-0.2151739	0.3313255	37	36	3.4%	-0.22 [-0.86, 0.43]
NCT00414427	-0.8803853	0.2562751	33	34	4.2%	-0.88 [-1.38, -0.38]
Ozturk 2006	-0.1368758	0.2921525	23	24	3.8%	-0.14 [-0.71, 0.44]
Petrella 2015	-0.0355	0.2463161	34	32	4.3%	-0.04 [-0.52, 0.45]
Popov 1989	-1.088324	0.4184004	19	11	2.7%	-1.09 [-1.91, -0.27]
Ravaud 1999	-0.4619007	0.2061198	49	49	4.7%	-0.46 [-0.87, -0.06]
Raynauld 2003	0.1177483	0.2464029	33	33	4.3%	0.12 [-0.37, 0.60]
Schue 2011	-0.207736	0.6144019	5	5	1.7%	-0.21 [-1.41, 1.00]
Smith 2003	-0.3261666	0.2395615	38	33	4.4%	-0.33 [-0.80, 0.14]
Yavuz 2012	-1.53523	0.234898	90	30	4.4%	-1.54 [-2.00, -1.07]
Young 2001	-0.3845994	0.3154607	21	20	3.6%	-0.38 [-1.00, 0.23]
Zhilyayev 2012	-0.4685471	0.1873348	67	52	4.9%	-0.47 [-0.84, -0.10]
Total (95% CI)			**922**	**827**	**100.0%**	**-0.40 [-0.58, -0.22]**

Heterogeneity: Tau² = 0.14; Chi² = 78.14, df = 25 (P < 0.00001); I² = 68%

Test for overall effect: Z = 4.29 (P < 0.0001)

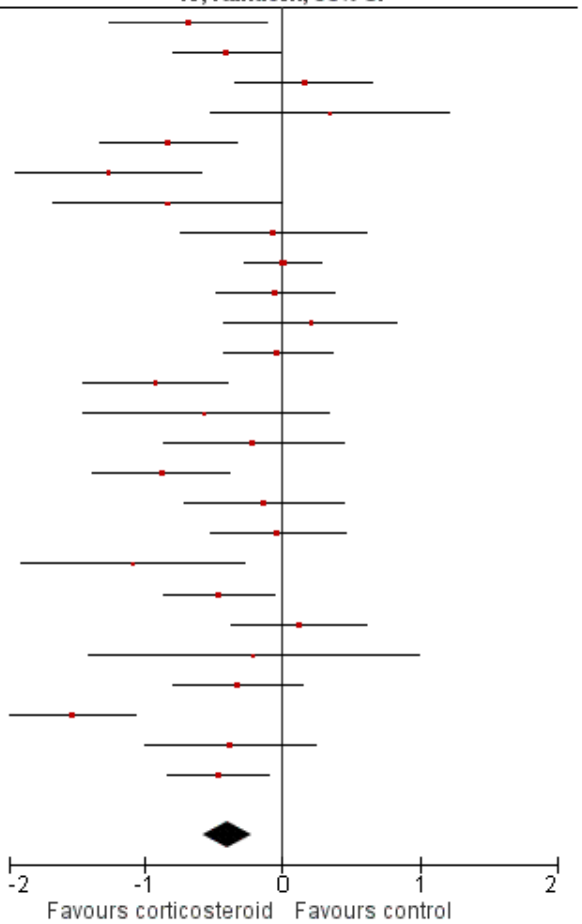
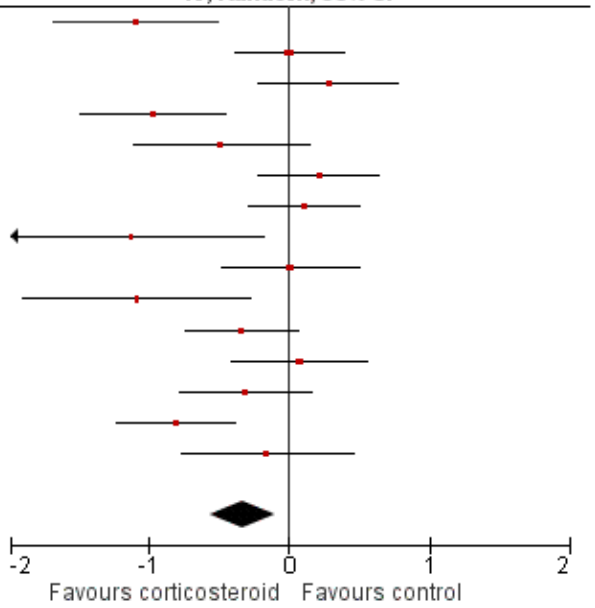


Figure 6. Forest plot of comparison: 2 Function, outcome: 2.1 Function - Main.

Study or Subgroup	Std. Mean Difference	SE	IA Corticosteroid Total	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Beyaz 2012	-1.09887	0.304267	25	25	6.1%	-1.10 [-1.70, -0.50]
Campos 2013	-0.0041622	0.1970754	52	51	7.9%	-0.00 [-0.39, 0.38]
Castro 2007	0.275871	0.255377	32	30	6.9%	0.28 [-0.22, 0.78]
Chao 2010	-0.972491	0.2669457	32	31	6.7%	-0.97 [-1.50, -0.45]
Di Sante 2012	-0.4867452	0.321119	20	20	5.9%	-0.49 [-1.12, 0.14]
Gaffney 1995	0.208693	0.218826	42	42	7.5%	0.21 [-0.22, 0.64]
Henriksen 2015	0.099827	0.200127	50	50	7.9%	0.10 [-0.29, 0.49]
Lyons 2005	-1.130546	0.4852872	10	10	3.8%	-1.13 [-2.08, -0.18]
Petrella 2015	0.006267	0.246184	33	33	7.1%	0.01 [-0.48, 0.49]
Popov 1989	-1.088324	0.4184004	19	11	4.6%	-1.09 [-1.91, -0.27]
Ravaud 1999	-0.3433526	0.2039811	49	49	7.8%	-0.34 [-0.74, 0.06]
Raynauld 2003	0.06595	0.246252	33	33	7.1%	0.07 [-0.42, 0.55]
Smith 2003	-0.31211	0.239426	38	33	7.2%	-0.31 [-0.78, 0.16]
Yavuz 2012	-0.8096383	0.2178688	90	30	7.6%	-0.81 [-1.24, -0.38]
Young 2001	-0.1579081	0.3129516	21	20	6.0%	-0.16 [-0.77, 0.46]
Total (95% CI)			**546**	**468**	**100.0%**	**-0.33 [-0.56, -0.09]**

Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 45.88$, df = 14 ($P < 0.0001$); $I^2 = 69\%$

Test for overall effect: $Z = 2.70$ ($P = 0.007$)



Rheumatol Int (2012) 32:3391–3396
DOI 10.1007/s00296-011-2188-0

ORIGINAL ARTICLE

Efficacy comparisons of the intraarticular steroidal agents in the patients with knee osteoarthritis

Umut Yavuz · Sami Sökücü · Akif Albayrak · Kahraman Öztürk

Table 1 The basic characteristic features of the patients according to treatment groups and statistical comparison of mean values

	Placebo ($n = 30$)	Triamsinolon ($n = 30$)	Betametazone ($n = 30$)	Methylprednisolone ($n = 30$)	P
Age	60 ± 6.1	60 ± 5.9	60 ± 6.3	61 ± 6.3	0.984
Sex	11 M/19 W	11 M/19 W	10 M/20 W	12 M/18 W	0.963
KLGS (mean)	3.07 ± 0.8	3.03 ± 0.8	3.13 ± 0.8	3.1 ± 0.8	0.891

Table 2 Mean change over time in the clinical variables (pain by 100-mm visual analog scale [VAS], global assessment [VAS], and Lequesne's functional index score) in each treatment group.

	VAS					LFS				
	Preenj.	Week 1	Week 3	Week 6	Week 12	Preenj.	Week 1	Week 3	Week 6	Week 12
Placebo	7.6 ± 1.6	6.1 ± 1.4	6.6 ± 1.6	7.3 ± 1.6	7.4 ± 1.7	14.9 ± 4.1	12.6 ± 3.9	13.2 ± 3.9	13.9 ± 4.0	14.5 ± 4.0
Triamsinolon	7.5 ± 1.5	4.3 ± 1.1	4.4 ± 1.3	5.2 ± 1.2	5.7 ± 1.5	14.7 ± 3.8	9.9 ± 3.0	10.6 ± 3.2	11.3 ± 3.4	12.0 ± 3.4
Betametazone	7.6 ± 1.6	4.1 ± 1.3	4.5 ± 1.2	5.2 ± 1.5	5.6 ± 1.2	15.0 ± 4.2	9.4 ± 3.4	10.0 ± 3.2	11.0 ± 3.6	11.8 ± 3.5
Methylprednisolone	7.7 ± 1.6	3.07 ± 1.4	3.4 ± 1.4	4.3 ± 1.4	5.0 ± 1.3	15.2 ± 4.1	8.4 ± 3.2	9.3 ± 3.2	10.1 ± 3.1	11.3 ± 3.5

Values are the mean ± SD. W1, W3, W6, and W12

Effetto citotossico degli anestetici + steroidi sui condrociti

Clin Orthop Relat Res (2010) 468:3112–3120
DOI 10.1007/s11999-010-1443-0

BASIC RESEARCH

Increased Chondrocyte Death after Steroid and Local Anesthetic Combination

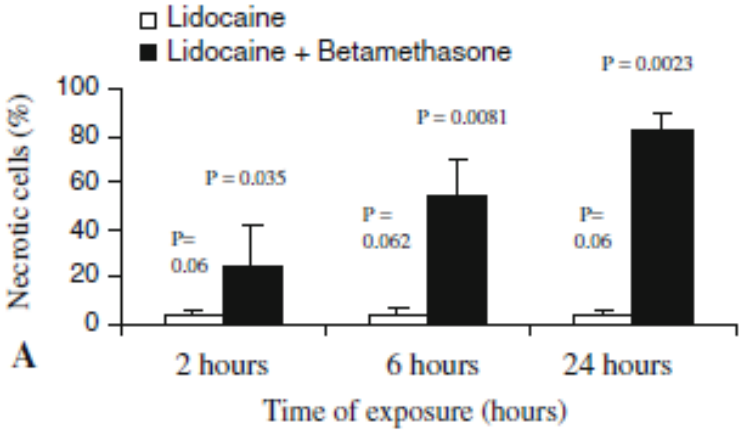
Boglárka Farkas MD, Krisztián Kvell MD, PhD, Tamás Czömpöly MD, PhD, Tamás Illés MD, PhD, Tamás Bárdos MD, PhD

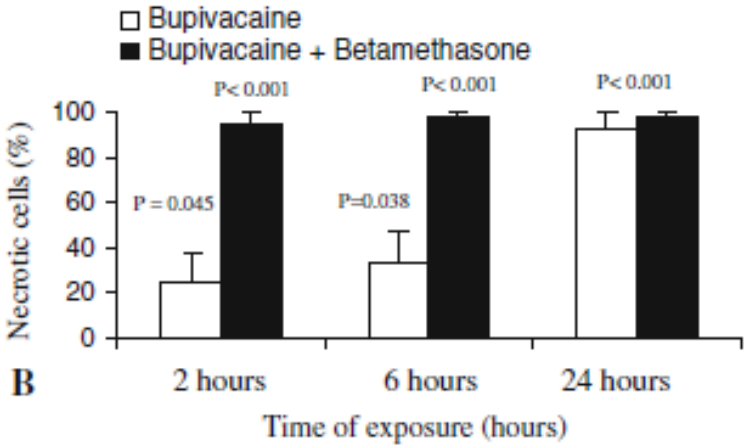
Methods Cell viability and apoptosis/necrosis assessment of human articular chondrocytes were performed in vitro (chondrocyte cell cultures) and ex vivo (osteochondral specimens) using flow cytometry and TUNEL analysis, respectively.

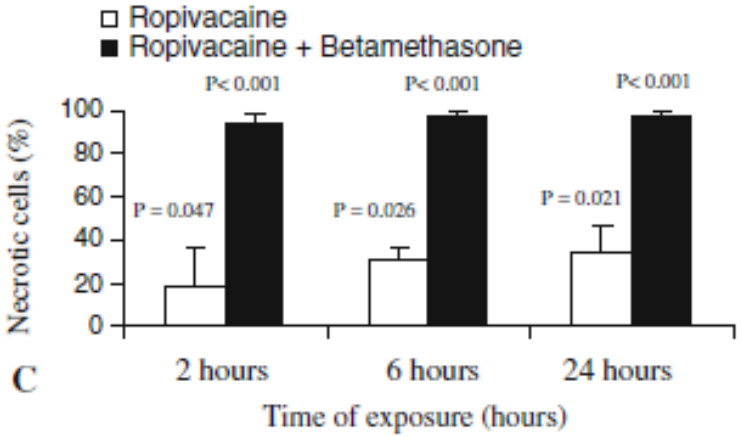
Table 1. Solutions and combinations used in the experiments*

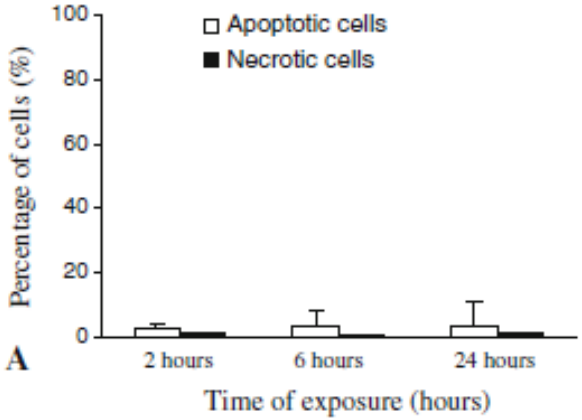
Agent	Concentration	Group number								
		I	II	III	IV	V	VI	VII	VIII	IX
Betamethasone	7 mg/mL	X					X	X	X	
Prednisolone	25 mg/mL		X							X
Lidocaine	10 mg/mL			X			X			X
Bupivacaine	5 mg/mL				X			X		
Ropivacaine	7.5 mg/mL					X			X	

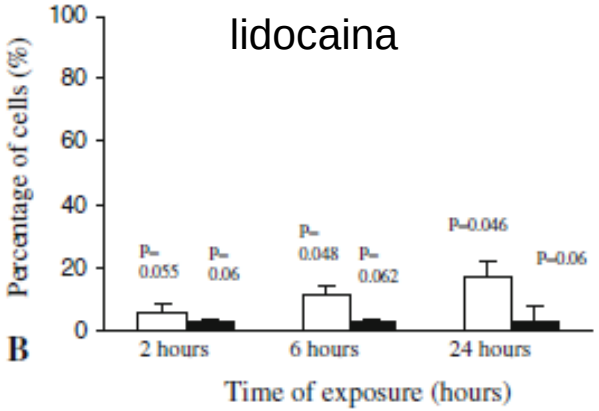
* Different steroids and local anesthetics were used alone or in combinations.

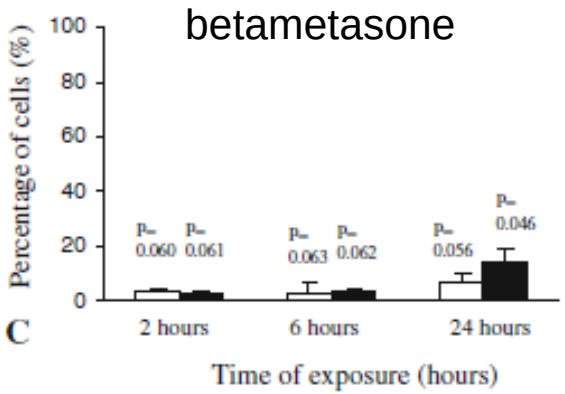

Lidocaine
Lidocaine + Betamethasone
Necrotic cells (%)
100
80
60
40
20
0
P= 0.06
P = 0.035
P = 0.062
P = 0.0081
P= 0.06
P = 0.0023
2 hours
6 hours
24 hours
Time of exposure (hours)
A

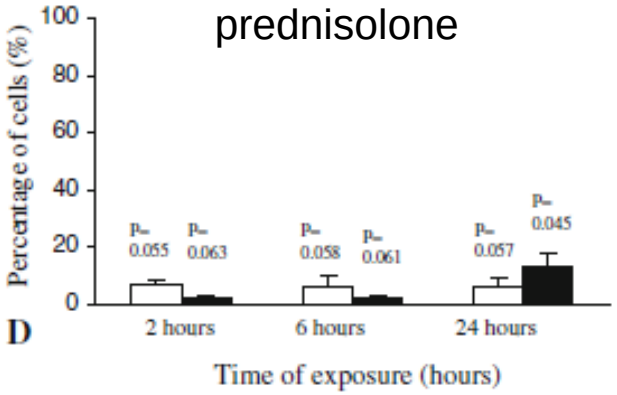

Bupivacaine
Bupivacaine + Betamethasone
Necrotic cells (%)
100
80
60
40
20
0
P = 0.045
P< 0.001
P=0.038
P< 0.001
P< 0.001
2 hours
6 hours
24 hours
Time of exposure (hours)
B

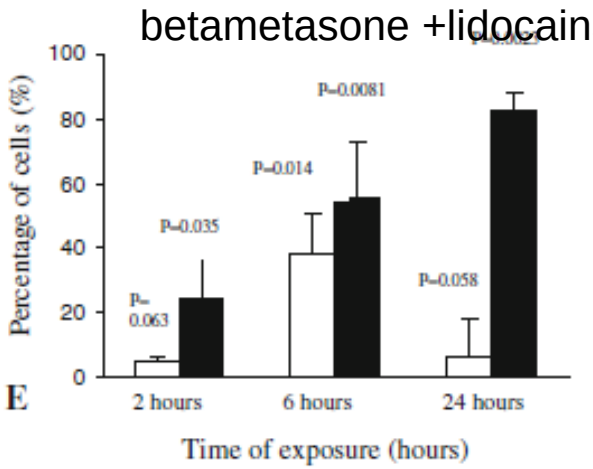

Ropivacaine
Ropivacaine + Betamethasone
Necrotic cells (%)
100
80
60
40
20
0
P = 0.047
P< 0.001
P = 0.026
P< 0.001
P = 0.021
P< 0.001
2 hours
6 hours
24 hours
Time of exposure (hours)
C


Apoptotic cells
Necrotic cells
Percentage of cells (%)
100
80
60
40
20
0
2 hours
6 hours
24 hours
Time of exposure (hours)
A


lidocaina
Percentage of cells (%)
P=0.055
P=0.06
P=0.048
P=0.062
P=0.046
P=0.06
2 hours
6 hours
24 hours
Time of exposure (hours)
B


betametasone
Percentage of cells (%)
P=0.060
P=0.061
P=0.063
P=0.062
P=0.056
P=0.046
2 hours
6 hours
24 hours
Time of exposure (hours)
C


prednisolone
Percentage of cells (%)
P=0.055
P=0.063
P=0.058
P=0.061
P=0.057
P=0.045
2 hours
6 hours
24 hours
Time of exposure (hours)
D


betametasone +lidocaina
Percentage of cells (%)
P=0.063
P=0.035
P=0.014
P=0.0081
P=0.058
2 hours
6 hours
24 hours
Time of exposure (hours)
E

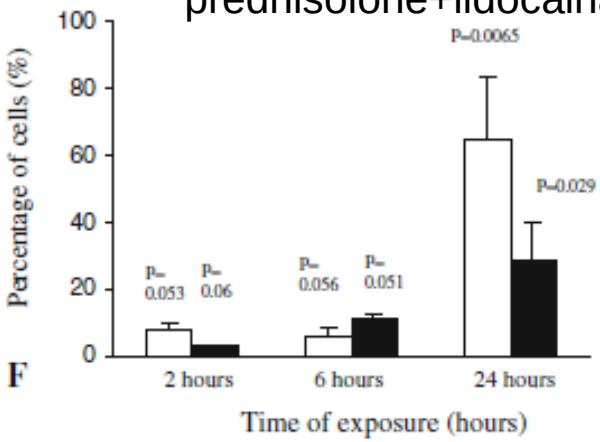

prednisolone+lidocaina
Percentage of cells (%)
P=0.053
P=0.06
P=0.056
P=0.051
P=0.0065
P=0.029
2 hours
6 hours
24 hours
Time of exposure (hours)
F

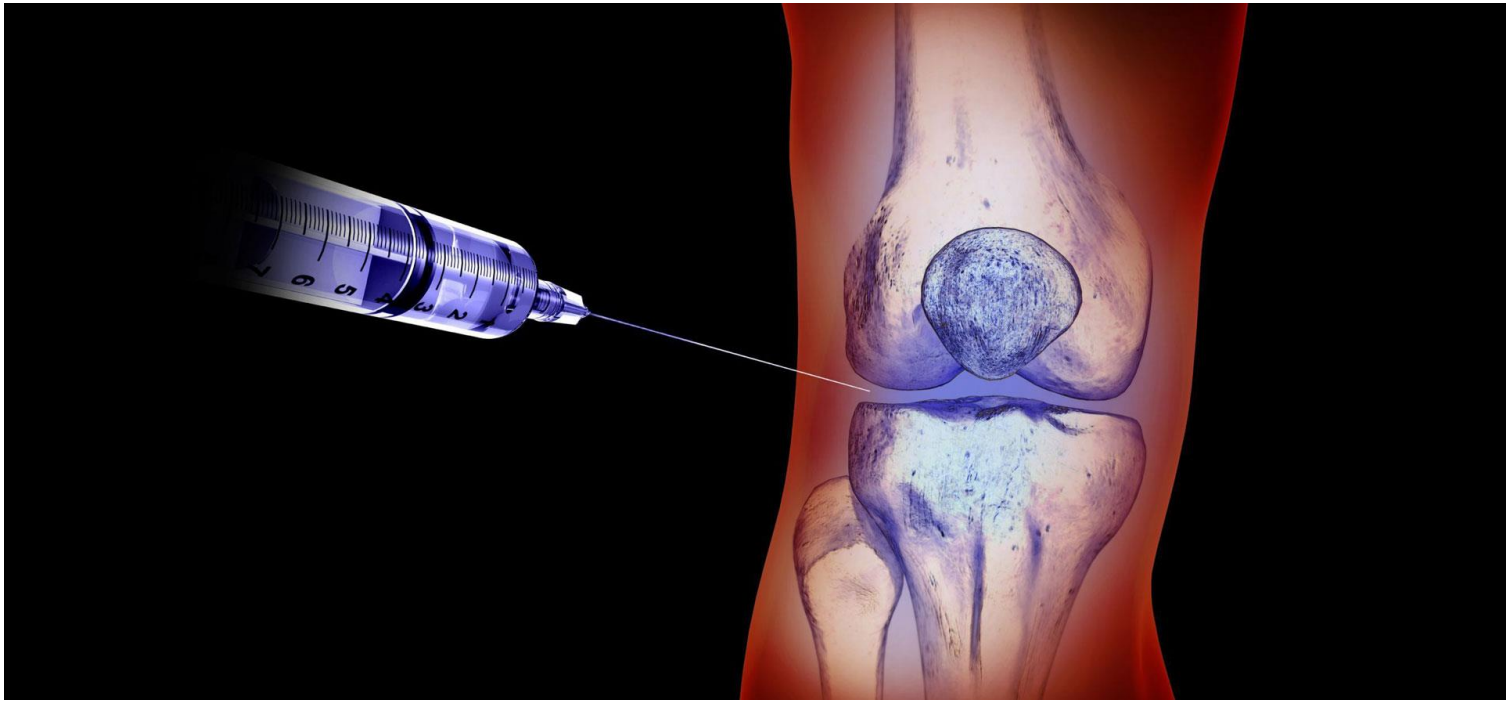
Table 2. Summary of findings from different studies

Study	Cell type	Agent and concentration used for exposure	Time of assessment (time of exposure if different)	Cytotoxicity
Nakazawa et al. [34]	Human articular chondrocyte monolayer culture	Triamcinolone 10^{-4} mol/L	72 hours	10.4%
Fubini et al. [15]	Equine articular chondrocyte monolayer culture	Methylprednisolone 1×10^{9} pg/mL (2 mmol/L)	72 hours	96%
Chu et al. [7]	Bovine articular chondrocytes cultured in alginate beads	Bupivacaine 0.5%	1 hour (15-30-60 minutes)	99%
Piper & Kim [39]	Human articular chondrocyte monolayer culture	Bupivacaine 0.5%	24 hours (30 minutes)	62.6%
		Ropivacaine 0.5%	24 hours (30 minutes)	36.1%
Seshadri et al. [46]	Bovine articular chondrocytes cultured in alginate beads	Methylprednisolone 8 mg/mL	24 hours (60 minutes)	62.4%
		Methylprednisolone 8 mg/mL + lidocaine 1%	24 hours (60 minutes)	99%
Current study	Human articular chondrocyte monolayer culture	Betamethasone 7 mg/mL	24 hours	20%
		Lidocaine 10 mg/mL	24 hours	20%
		Ropivacaine 7.5 mg/mL	24 hours	39%
		Betamethasone 7 mg/mL + lidocaine 10 mg/mL	24 hours	83%
		Betamethasone 7 mg/mL + ropivacaine 7.5 mg/mL	24 hours	98%

TERAPIA INTRA-ARTICOLARE NELL' OA

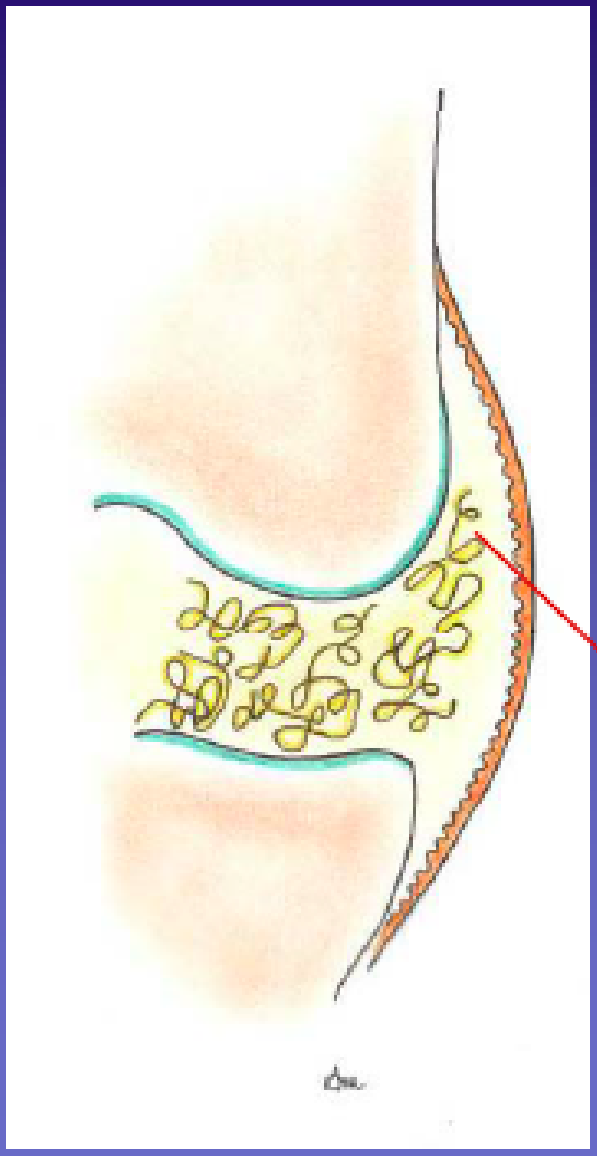
- TERAPIA INFILTRATIVA CON STEROIDI

- **TERAPIA INFILTRATIVA CON ACIDO IALURONICO**

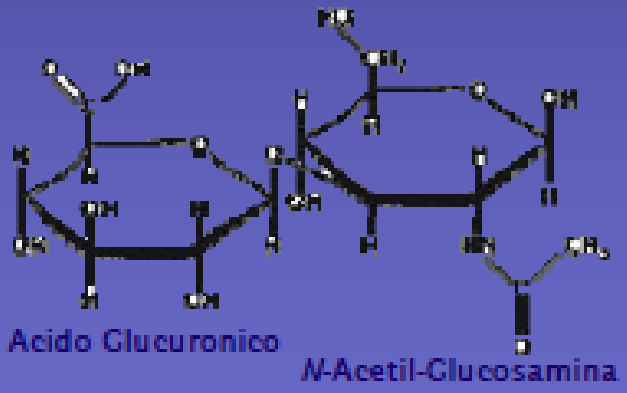


L'acido ialuronico (AI) è il principale responsabile delle caratteristiche viscoelastiche del liquido sinoviale.

Acido Ialuronico



- Sintetizzato dai sinoviociti B, garantisce l'attività di filtro della membrana sinoviale
- Bilancio idrico tissutale
- Interazioni steriche
- Lubrificazione



2000-10000 kDa - 0.5-4 mg/ml

Il peso molecolare e la concentrazione di AI nel liquido sinoviale sono diminuiti nell'OA

- Diluizione secondaria al versamento
- Degradazione dell'AI nel liquido sinoviale
- Alterata sintesi di AI

J Rheumatol Suppl. 1993 Aug;39:3-9.

Viscosupplementation: a new concept in the treatment of osteoarthritis.

Balazs EA, Denlinger JL.

Biomatrix Inc., Ridgefield, NJ 07657.

Il concetto di **viscosupplementazione** è basato sull'ipotesi che l'iniezione intra-articolare di AI può aiutare a ristabilire la viscoelasticità del liquido sinoviale, migliorando la funzionalità articolare e riducendo il dolore

Primi studi sull'efficacia

Trial randomizzati di AI vs Placebo nella OA del ginocchio

Dugadous et al. 1993	AI > P a 7 sett. e 12 mesi
Henderson et al. 1994	AI = P a 5 sett. e 5 mesi
Formiguera et al. 1995	AI > P dal 35° giorno al 3° mese
Altman et al. 1998	AI > P a 5 sett. e 6 mesi

Trial randomizzati di AI vs Corticosteroidi nella OA del ginocchio

Leardini et al. 1991	AI > CS dal 28° giorno al 2° mese
Jones et al. 1995	AI > CS dalla 5° sett. al 6° mese

L'osservazione che i risultati clinici superano il tempo di dimezzamento dell'AI esogeno intra-articolare (< 24 ore) supporta l'ipotesi che il solo ripristino delle proprietà reologiche non può spiegare gli effetti a lungo termine.

Effetto biologico
ed
anti-infiammatorio

Ghosh P. Clin Exp Rheumatol 1994, Kelly M.A. Am J Orthop 2004

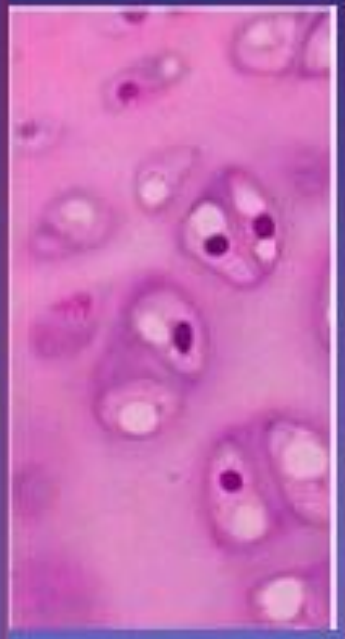
Effetti biologici dell'AI

Sulla matrice extracellulare

Riduzione rilascio PG dalla matrice cartilaginea (Morris et al. 1992)

Aumentata sintesi di condroitinsolfato (Kawasaki et al. 1999)

Aumentata sintesi PG in presenza di IL-1α (Stöve et al. 2002)



Sulla cartilagine

Soppressione degenerazione cartilaginea (Listrat et al. 1997)

Miglioramento strato superficiale cartilagineo e riduzione infiammazione sinoviale (Frizziero et al. 1998)

Aumento densità e miglioramento morfologia condrociti (Guidolin et al. 2001)

Effetti biologici dell'AI

Sui mediatori dell'infiammazione

Riduzione dei livelli di PGE_2 nel LS (Punzi et al. 1989)

Aumentata produzione di TIMP-1 (Yasui et al. 1992)

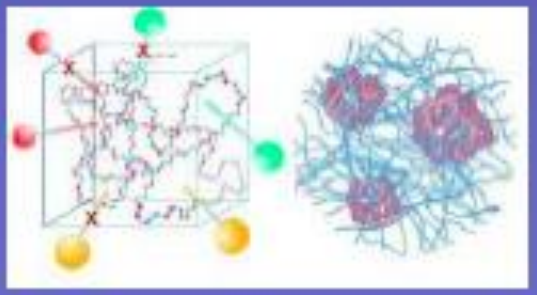
Riduzione espressione IL-1α e stromelisina e produzione NO (Takahashi et al. 1999, 2001, Kobayashi et al. 2004)

Soppressione produzione TNF-α (Comer et al. 1996)

Sulle cellule immunitarie

Riduzione attivazione e migrazione leucociti PMN (Partsch et al. 1989)

Soppressione adesione ed aggregazione neutrofila (Forrester & Lackie 1981)



Effetti biologici dell'AI

Sono mediati da specifici recettori situati sulla superficie di diverse cellule. Alcuni di questi sono stati ben caratterizzati: CD44, ICAM-I, RHAMM, …

Entwistle J. et al. J Cell Bioch 1996, Pohl M. et al. Dev Biol 2000

Attività biologiche dell'AI e peso molecolare

- AI a basso/medio peso molecolare

Attività reologica/ analgesica

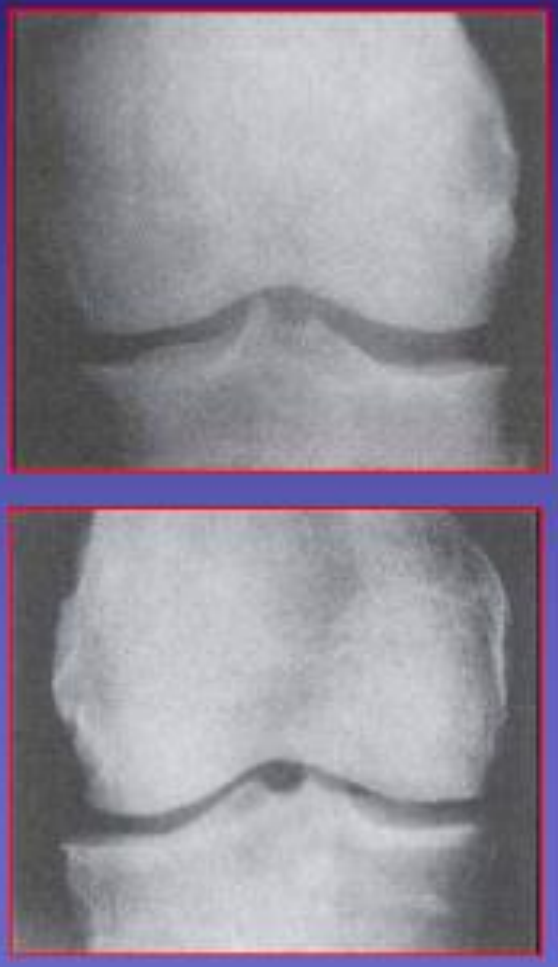
Attività biologica

- AI ad alto peso molecolare

Attività reologica/ analgesica

Attività biologica?

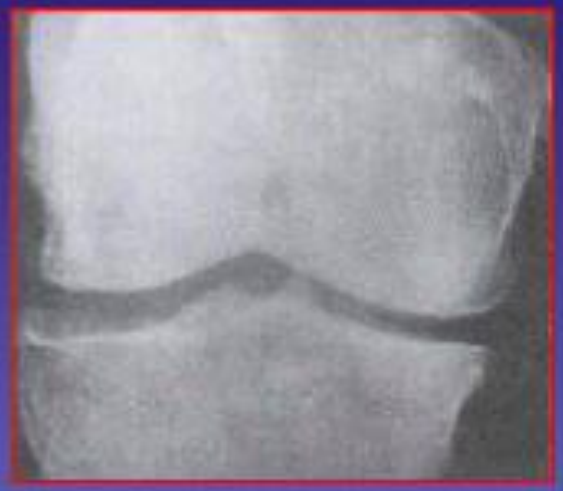
Quale stadio trattare e con quale preparato?

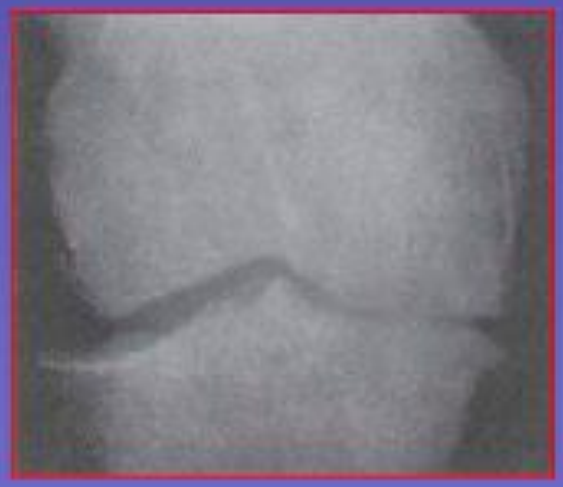


AI a basso/medio peso molecolare

- Azione analgesica e antinfiammatoria
- **Disease modifyng**

Quale stadio trattare e con quale preparato?





AI ad alto peso molecolare

- Azione analgesica e antinfiammatoria
- ?

Terapia loco-regionale: finalità

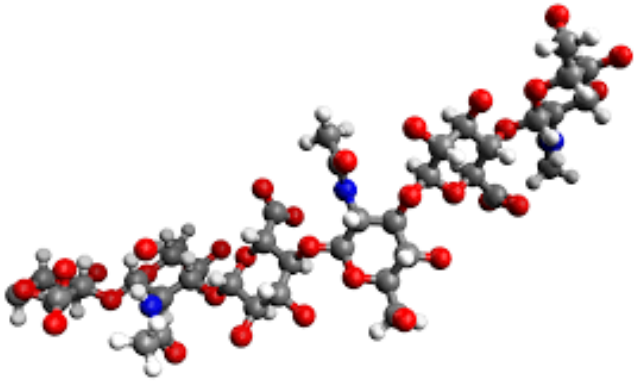
- **Potenziamento dell'effetto terapeutico per aumento della concentrazione locale del principio attivo**

- **Riduzione degli effetti collaterali a livello sistemico**

Indicazioni all'uso di acido ialuronico intra-articolare

- Dolore resistente ad altre terapie farmacologiche (grado radiologico II-III)
- OA sintomatica ed evoluta (grado IV) e controindicazioni alla protesizzazione
- OA sintomatica in pazienti in cui i FANS siano controindicati o intollerati

HA in commercio



La maggior parte degli HA commerciali ha struttura analoga a quello endogeno a parte quelle ad alto peso molecolare che presenta cross-link intramolecolari determinanti una maggior elasto-viscosità.

Sostanzialmente si dividono a seconda del peso molecolare in basso(500-1200 kDa), medio (1200-2000kDa) ed alto peso molecolare (6000 KDa cross-linked).

Table 1 Preparations of intra-articular hyaluronic acid (HA) and hylan available in Europe and/or the USA

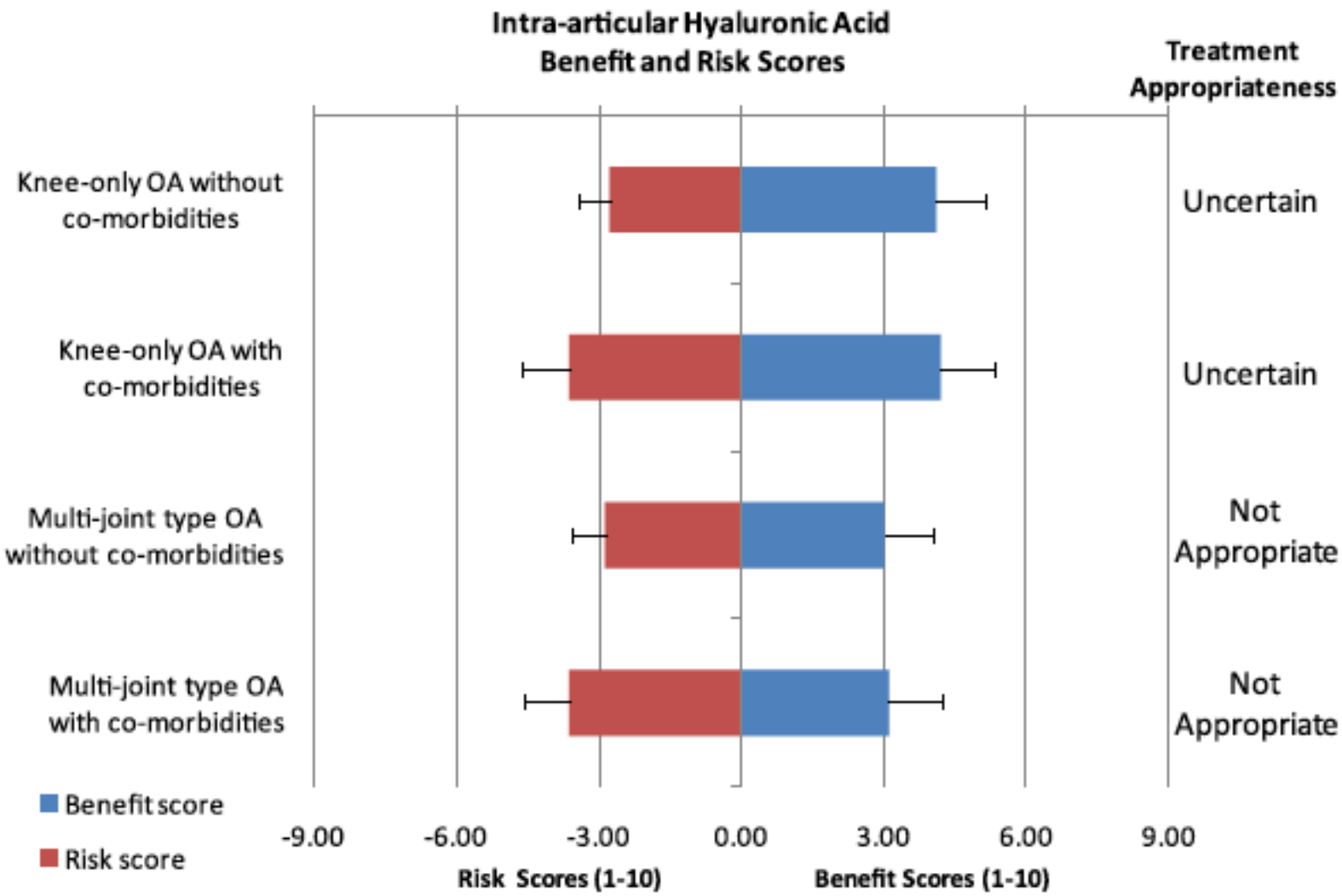
Tradename	Concentration (mg/ml)	Generic name	Source (type)	Molecular weight (kDa)
Adant®	25 mg/2.5 ml	Sodium hyaluronate	Biofermentation	900
Arthrum®	40 mg/2 ml	Sodium hyaluronate	Biofermentation	2,400
Artz®/Supartz®	25 mg/2.5 ml	Sodium hyaluronate	Rooster combs (avian)	600–1,200
Coxarthrum®	75 mg/3 ml	Sodium hyaluronate	Biofermentation	2,400
Durolane®	20 mg/3 ml	Sodium hyaluronate	Biofermentation	NA
Erectus®	NA	NA	NA	1,100
Euflexxa®	20 mg/2 ml	Sodium hyaluronate	Biofermentation	2,400–3,600
Fermathron®	20 mg/2 ml	Sodium hyaluronate	Biofermentation	1,000
Go-On®	25 mg/2.5 ml	Sodium hyaluronate	Biofermentation	800–1,200
Go-On® Mini	10 mg/1 ml			
Hyalart®	20 mg/2 ml	Sodium hyaluronate	Rooster com	500–730
Hyalgan®	20 mg/2 ml	Sodium hyaluronate	Rooster c	00–730
Hyalubrix®	30 mg/2 ml	Sodium hyaluronate	Bioferme	1,500
Intragel® 0.8%	16 mg/2 ml	Sodium hyaluronate	Biofermen	00–1,200
Intragel® 1.6%	32 mg/2 ml			
Jointex®	16 mg/2 ml	Sodium hyaluronate	iofermentation	00–1,200
Jointex® Starter	32 mg/2 ml			
MonoVisc®	20 mg/ml	Sodium hyaluronat	Biofermentation, lightly cross-link	NA
NeoVisc®	20 mg/2 ml	Sodium hyaluron	Biofermentation	1,000
Orthovisc®	30 mg/2 ml	High molecular v	luronan n/chemical modifi	1
Orthovisc® mini	15 mg/1 ml			
Ostenil®	20 mg/2 ml	Sodium hyaluron		
Ostenil® mini	10 mg/ml			
RenehaVis®	7 mg/0.7 ml +	Sodium hyaluronate	Biofermentat	1,000
	15.4 mg/0.7 ml			2,000
Sinovial®	16 mg/2 ml	Sodium hyaluronate	Biofermentati	800–1,200
Sinovial® Mini	8 mg/1 ml			
Sinovial® Forte	32 mg/2 ml			
SportVis®	12 mg/1.2 ml +	Sodium hyaluronate		NA
Suplasyn®	20 mg/2 ml	Sodium hyaluronate	Biofermentation	500–730
Suplasyn® m.d.	7 mg/0.7 ml			
Synocrom®	20 mg/2 ml	Sodium hyaluronate	Biofermentation	1,600
Synocrom® mini	10 mg/1 ml			2,100
Synocrom® forte	40 mg/2 ml			
Synvisc®	16 mg/2 ml	Hylan G-F 20	Rooster combs (avian), cross-linked	6,000
Synvisc® One	48 mg/6 ml			
Viscorneal-ortho®	20 mg/2 ml	Sodium hyaluronate	Rooster combs (avian)	6,000
Yaral®	16 mg/2 ml	Sodium hyaluronate	Biofermentation	800–1,200
Yaral® Mini	8 mg/1 ml			
Yaral® Forte	32 mg/2 ml			

Efficacia terapia intra-articolare con HA

Osteoarthritis and Cartilage

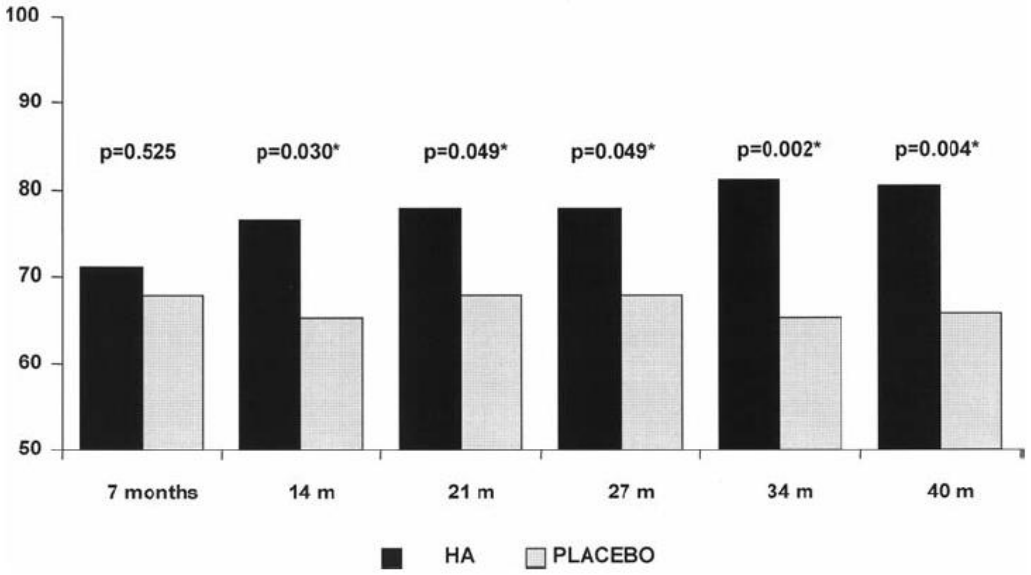
OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

OARSI guidelines for the non-surgical management of knee osteoarthritis


Intra-articular Hyaluronic Acid
Benefit and Risk Scores
Treatment Appropriateness
Knee-only OA without co-morbidities
Uncertain
Knee-only OA with co-morbidities
Uncertain
Multi-joint type OA without co-morbidities
Not Appropriate
Multi-joint type OA with co-morbidities
Not Appropriate
Benefit score
Risk score
-9.00
-6.00
-3.00
0.00
3.00
6.00
9.00
Risk Scores (1-10)
Benefit Scores (1-10)

A 40-month multicentre, randomised placebo-controlled study to assess the efficacy and carry-over effect of repeated intra-articular injections of hyaluronic acid in knee osteoarthritis: the AMELIA project

F Navarro-Sarabia,[1] P Coronel,[2] E Collantes,[3] F J Navarro,[4] A Rodriguez de la Serna,[5] A Naranjo,[6] M Gimeno,[7] G Herrero-Beaumont,[8] on behalf of the AMELIA study group



301 pazienti 109 con HA e 94 con placebo
Cicli di 5 settimane ogni 6 mesi
Grado radiologico II-III

Figure 3 Evolution of responders Osteoarthritis Research Society International, 2004. HA, hyaluronic acid.

Ann Rheum Dis 2011;**70**:1957–1962. doi:10.1136/ard.2011.152017

Studi di confronto terapia HA intra-articolare in OA del ginocchio vs NSAIDs

Relative efficacy of hyaluronic acid in comparison with NSAIDs for knee osteoarthritis: A systematic review and meta-analysis

Raveendhara R. Bannuru, MD, FAGE[a,b,*], Elizaveta E. Vaysbrot, MD, MS[a,b], Matthew C. Sullivan, BA[a,b], Timothy E. McAlindon, MD, MPH[a,b]

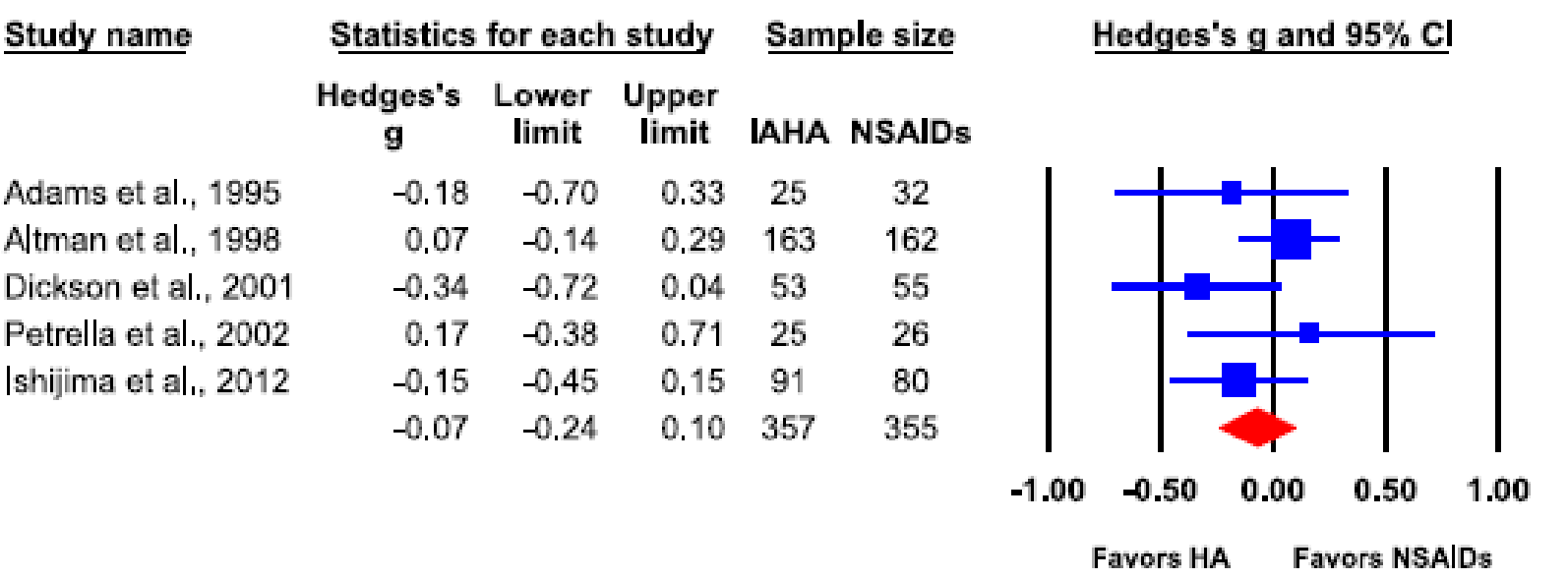
[a] *Center for Treatment Comparison and Integrative Analysis (CTCIA), Tufts Medical Center, 800 Washington St. #63, Boston, MA 02111*
[b] *Division of Rheumatology, Tufts Medical Center, Boston, MA*

Table 1
Study characteristics

Study	Treatment	Dose	*n*	Age (yr)	Female (%)	BMI	Duration (wk)	Main outcomes
Adams et al. [26], USA	IAHA	3 weekly IA injections	25	61	68	27.0	12	VAS pain with motion
	Usual NSAID therapy	Usual dose (× 12 wk) + 3 weekly arthrocenteses	32	63	68	23.7		
Altman and Moskowitz [27], USA	IAHA	5 weekly IAHA injections + oral placebo	163	62	61	31.5	26	VAS pain on walking and WOMAC pain, function, and stiffness
	Naproxen	500 mg orally twice daily (× 12 wk) + 5 weekly IA saline injections	162	63	57	31.9		
Dickson et al. [28], UK	IAHA	3 weekly IA injections + oral placebo	53	65	57	29.0	12	WOMAC pain, function, and stiffness and Lequesne index
	Diclofenac	100 mg orally once daily (× 12 wk) +3 weekly arthrocenteses	55	64	55	29.0		
Petrella et al. [29], Canada	IAHA	3 weekly IA injections + oral placebo	25	67	36	29.5	12	WOMAC pain, function, and stiffness and VAS pain on walking
	Diclofenac	75 mg and 100 μg misoprostol orally twice daily (× 12 wk) + 3 weekly IA saline injections	26	66	42	29.4		
Ishijima et al. [30], Japan	IAHA	5 weekly IA injections	91	nd	nd	nd	5	VAS pain
	Loxoprofen	60 mg orally thrice daily (× 5 wk)*	80	nd	nd	nd		

Note: IA = intra-articular; IAHA= intra-articular hyaluronic acid; wk = weeks; yr = year; BMI = body mass index; VAS = visual analog scale; WOMAC = Western Ontario & McMaster Universities Osteoarthritis Index; nd = no data.

* No injection control.



Q-value = 4.8; P = 0.31; I^2 = 16%

Fig. 2. Forest plot for pain at the end of trial.

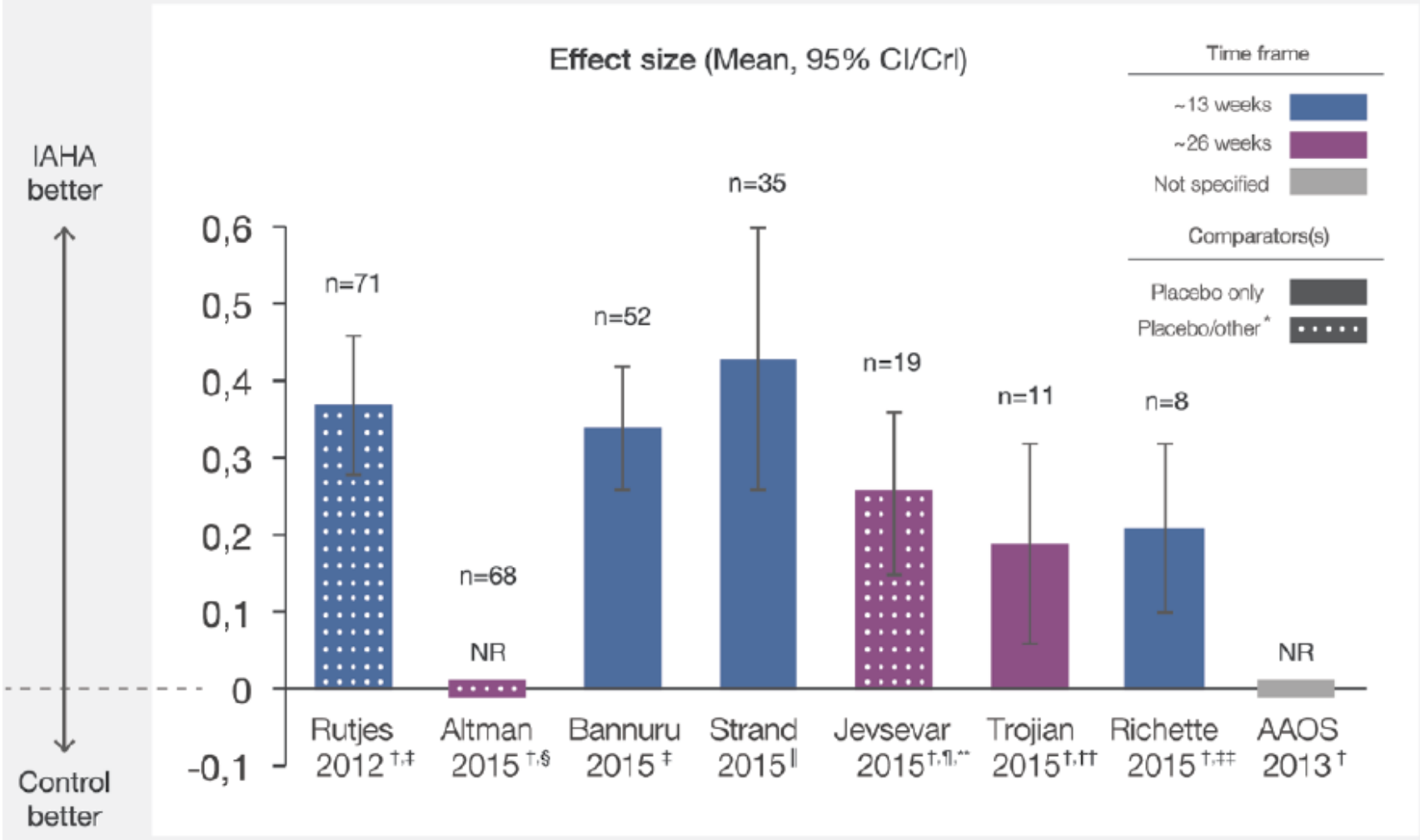
Conclusion

This meta-analysis showed that IAHA injection was not statistically significantly different in terms of efficacy for symptomatic knee OA from continuous oral NSAIDs at 4 weeks, 12 weeks, and end of the trial. Given the favorable safety profile of IAHA over NSAIDs, this result suggests that IAHA may be a viable alternative to NSAIDs in knee OA care, especially for older patients at greater risk for systemic adverse events. Studies evaluating the synergistic effect of the two treatments remain of importance.

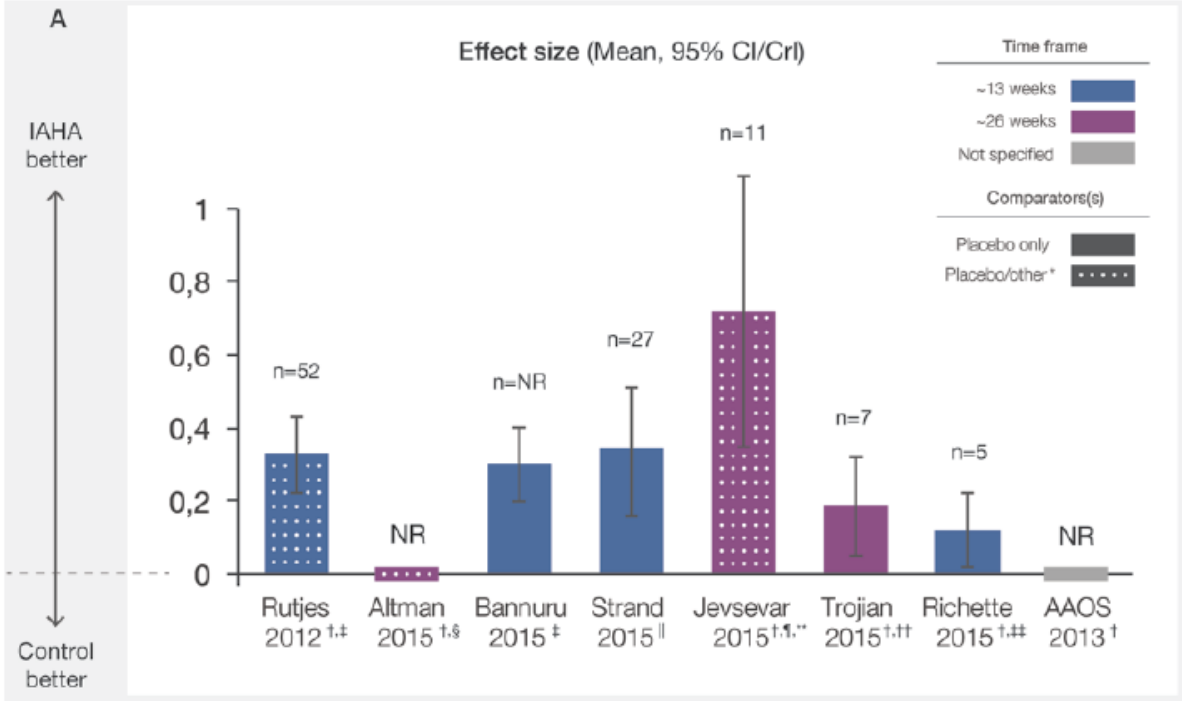
Therapeutic Advances in Musculoskeletal Disease

Intra-articular hyaluronic acid in the treatment of knee osteoarthritis: a Canadian evidence-based perspective

Mohit Bhandari, Raveendhara R. Bannuru, Eric M. Babins, Johanne Martel-Pelletier, Moin Khan, Jean-Pierre Raynauld, Renata Frankovich, Deanna Mcleod, Tahira Devji, Mark Phillips, Emil H. Schemitsch and Jean-Pierre Pelletier

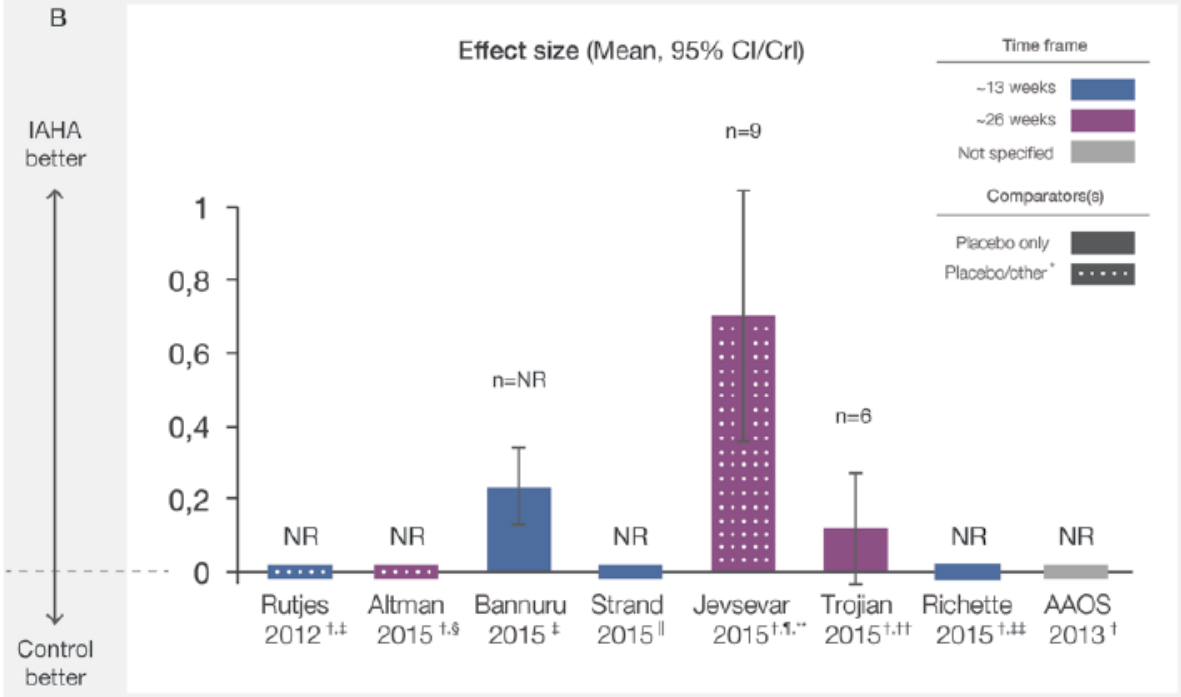


Publication status	Published/ unpublished	Published	Published/ unpublished	Published	Published	Published	Published	Published
Study type	Larger, Quasi-randomized /randomized	Larger, Randomized	Larger, Randomized	Moderate, Randomized	Moderate, Randomized	More restrictive, Randomized	More restrictive, Randomized	More restrictive, Randomized
MA restrictions	NA	NA	NA	US approved only	< 30 patients/ arm only	Clinically relevant only	Low risk of bias only	< 30 patients/ arm only



Function

Stiffness



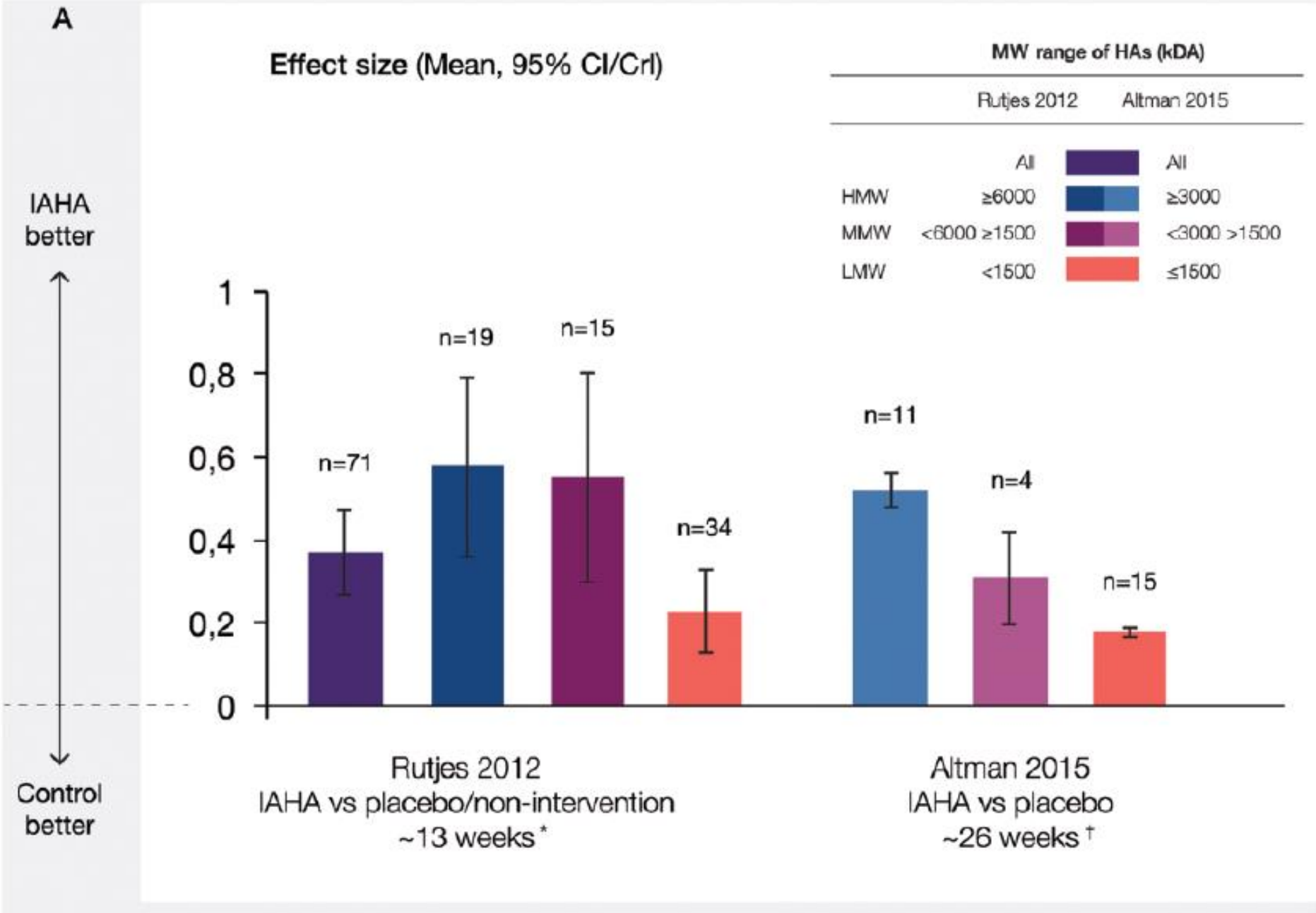
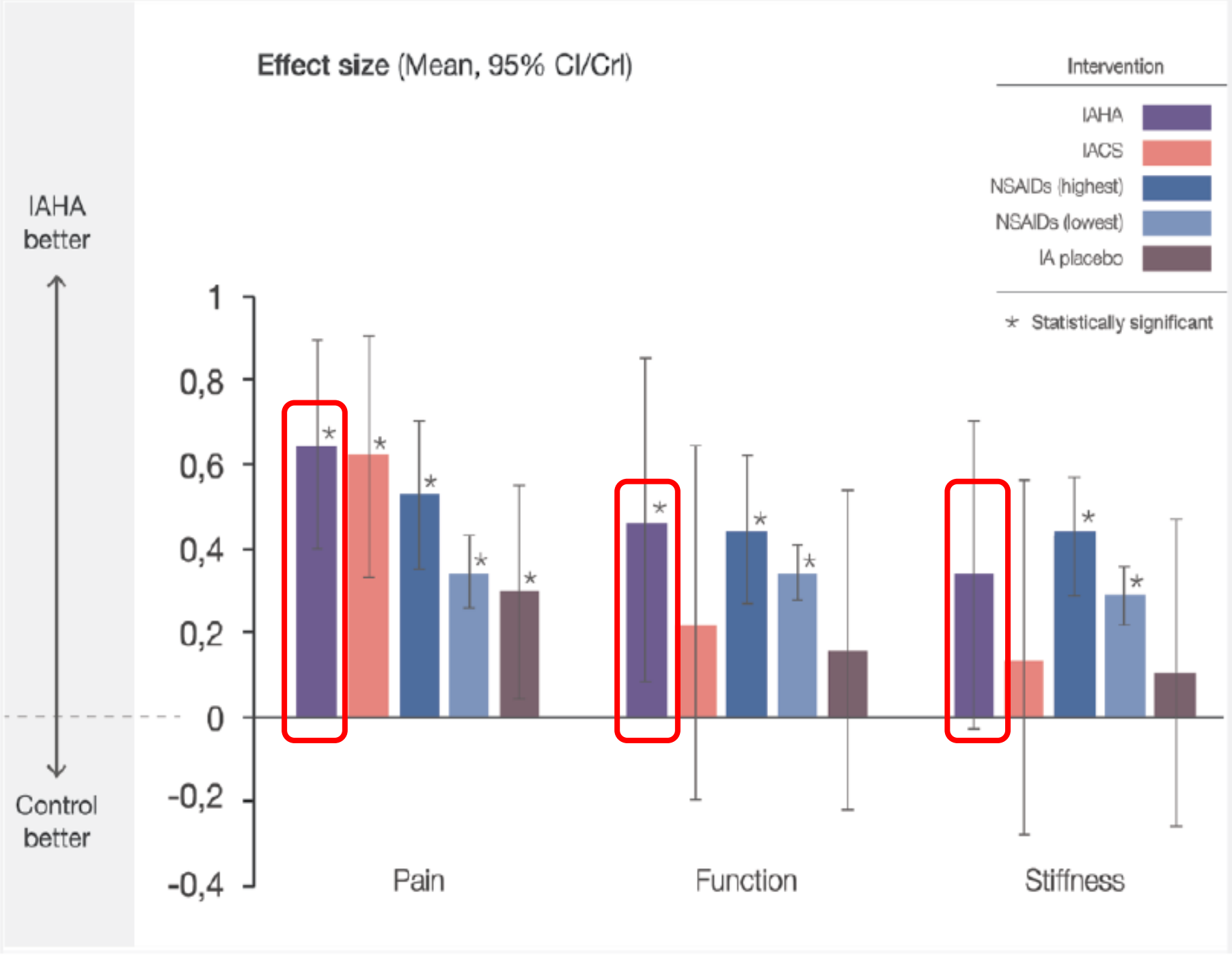
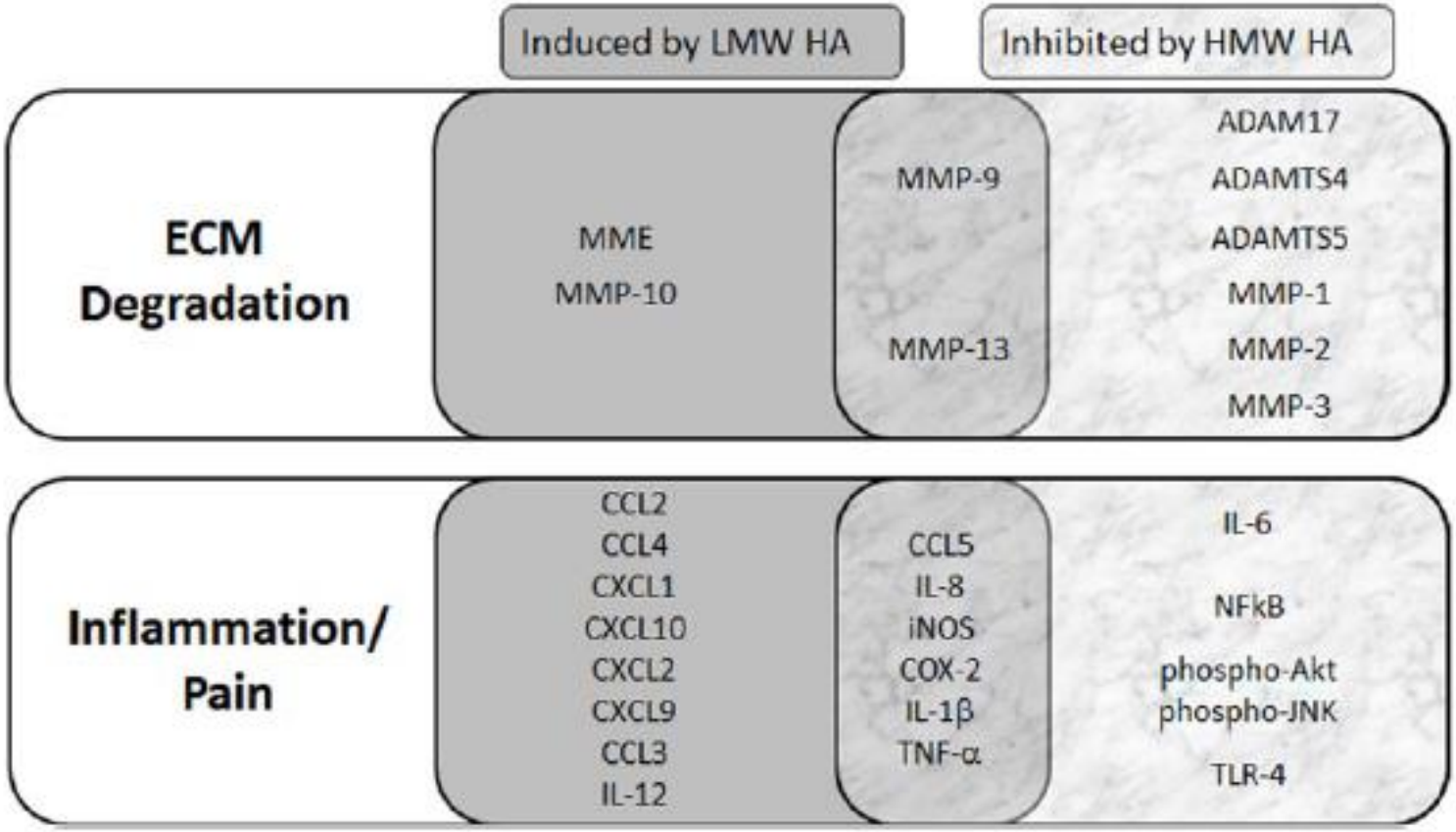

A
Effect size (Mean, 95% CI/CrI)
MW range of HAs (kDA)
Rutjes 2012
Altman 2015
All
All
HMW
≥6000
≥3000
MMW
<6000 ≥1500
<3000 >1500
LMW
<1500
≤1500
IAHA better
Control better
1
0,8
0,6
0,4
0,2
0
n=71
n=19
n=15
n=34
n=11
n=4
n=15
Rutjes 2012
IAHA vs placebo/non-intervention
~13 weeks *
Altman 2015
IAHA vs placebo
~26 weeks †

Table 1. Safety outcomes of IAHA therapy from recent meta-analyses. Any AEs, local reactions, serious AEs and withdrawal rates are reported, with additional data for derivation method and intrinsic HA properties when available.

	Rutjes 2012[20]	Bannuru 2015[17]	Altman 2016[16]	Strand 2015[21]
	Relative risk (95% CI), [trials]	**Median event rates (interquartile range), % [trials] IAHA vs IAP**	**Pooled incidence % (95% CI)**	**Absolute risk difference, % (95% CI), [trials]**
Any AEs	1.04 (0.99–1.09), $p = 0.158$ [$n = 25$]	16 (54.6) vs 21.7 (56.0), [$n = 35$]	NR	NR
Local AE/ injection site flare-ups*	Local AE 1.34 (1.13–1.60) $p = 0.001$, [$n = 31$] Injection site flare up subgroup 1.51 (0.84–2.72) $p = 0.165$, [$n = 6$]	Local AE 8.4 (14.4) vs 4.7 (16.1), [$n = 39$]	Injection site flare-ups AD-HA > Bio-HA 13.19 (12.04–14.44) vs 3.04 (2.34–3.95), $p \leqslant 0.001$ HMW (⩾3000 kDa) > LMW (⩽1500 kDa) 13.73 (12.33–15.27) vs 10.73 (9.27–12.39), $p = 0.007$	NR
Overall SAEs	1.41 (1.02–1.97) $p = 0.039$ [$n = 14$]	0 (0.9) vs 0 (0), [$n = 36$] Septic joint 0 (0) vs 0 (0), [$n = 18$]	NR	0.7 (–0.2–1.5), $p = 0.12$ [$n = 28$]
Withdrawals due to AEs	1.33 (1.01–1.74) $p = 0.04$ [$n = 23$]	0.9 (3.9) vs 1.0 (2.6), [$n = 36$]	Withdrawals due to treatment-related AEs AD-HA vs BIO-HA 1.49 (1.05–2.12) vs 1.00 (0.73–1.37), $p = 0.09$ HMW (⩾3000 kDa) vs LMW (⩽1500 kDa) 0.77 (0.48–1.21) vs 2.20 (1.70–2.84), $p = 0.004$	0.2 (–0.4–0.8), $p = 0.46$ [$n = 31$]


Effect size (Mean, 95% CI/CrI)
Intervention
IAHA
IACS
NSAIDs (highest)
NSAIDs (lowest)
IA placebo
* Statistically significant
IAHA better
Control better
1
0,8
0,6
0,4
0,2
0
-0,2
-0,4
Pain
Function
Stiffness


Induced by LMW HA
Inhibited by HMW HA
ECM Degradation
MME
MMP-10
MMP-9
MMP-13
ADAM17
ADAMTS4
ADAMTS5
MMP-1
MMP-2
MMP-3
Inflammation/ Pain
CCL2
CCL4
CXCL1
CXCL10
CXCL2
CXCL9
CCL3
IL-12
CCL5
IL-8
iNOS
COX-2
IL-1β
TNF-α
IL-6
NFkB
phospho-Akt
phospho-JNK
TLR-4

The Journal of Rheumatology

The Journal of Rheumatology Volume 41, no. 5

Potential Role of Hyaluronic Acid on Bone in Osteoarthritis: Matrix Metalloproteinases, Aggrecanases, and RANKL Expression are Partially Prevented by Hyaluronic Acid in Interleukin 1-stimulated Osteoblasts

Zvezdana Mladenovic, Anne-Sophie Saurel, Francis Berenbaum and Claire Jacques

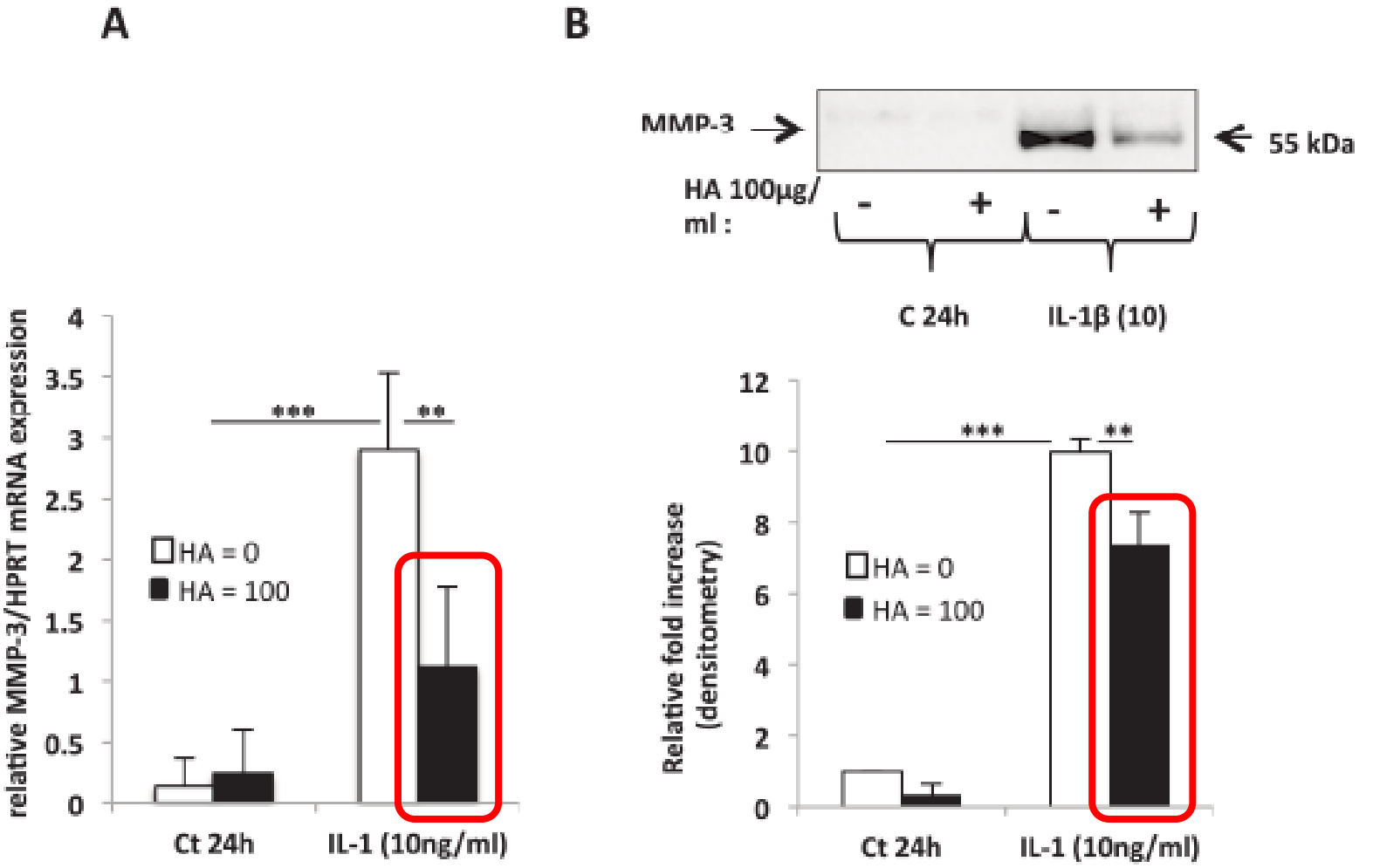


Figure 1. Effect of hyaluronan (HA) on interleukin 1β (IL-1β)-induced matrix metalloproteinase 3 (MMP-3) mRNA expression and protein release. Osteoblasts were treated for 7 days with or without HA (100 µg/ml). IL-1β (10 ng/ml) was added for the last 24 h. A. Quantitative PCR analysis of mRNA level of MMP-3. B. Western blot analysis of MMP-3 release into medium. Data are mean of 4 independent experiments analyzed in duplicate (corrected p values: ** < 0.01; *** < 0.001). HPRT: hypoxanthine phosphoribosyltransferase.

PLOS ONE

RESEARCH ARTICLE

Hyaluronic Acid Suppresses the Expression of Metalloproteinases in Osteoarthritic Cartilage Stimulated Simultaneously by Interleukin 1β and Mechanical Load

Florian Pohlig[1]*, Florian Guell[1], Ulrich Lenze[2], Florian W. Lenze[1], Heinrich M. L. Mühlhofer[1], Johannes Schauwecker[1], Andreas Toepfer[1], Philipp Mayer-Kuckuk[1], Rüdiger von Eisenhart-Rothe[1], Rainer Burgkart[1], Gian M. Salzmann[3]

1 Department of Orthopedic Surgery, Klinikum rechts der Isar, Technical University Munich, Ismaninger Str, 22, 81675 Munich, Germany, **2** Department of Traumatology, Universitätsspital Basel, Spitalstr. 21, 4031 Basel, Switzerland, **3** Division of Lower Extremity Surgery, Schulthess Klinik, Lengghalde 2, 8008 Zurich, Switzerland

* Florian.Pohlig@mri.tum.de

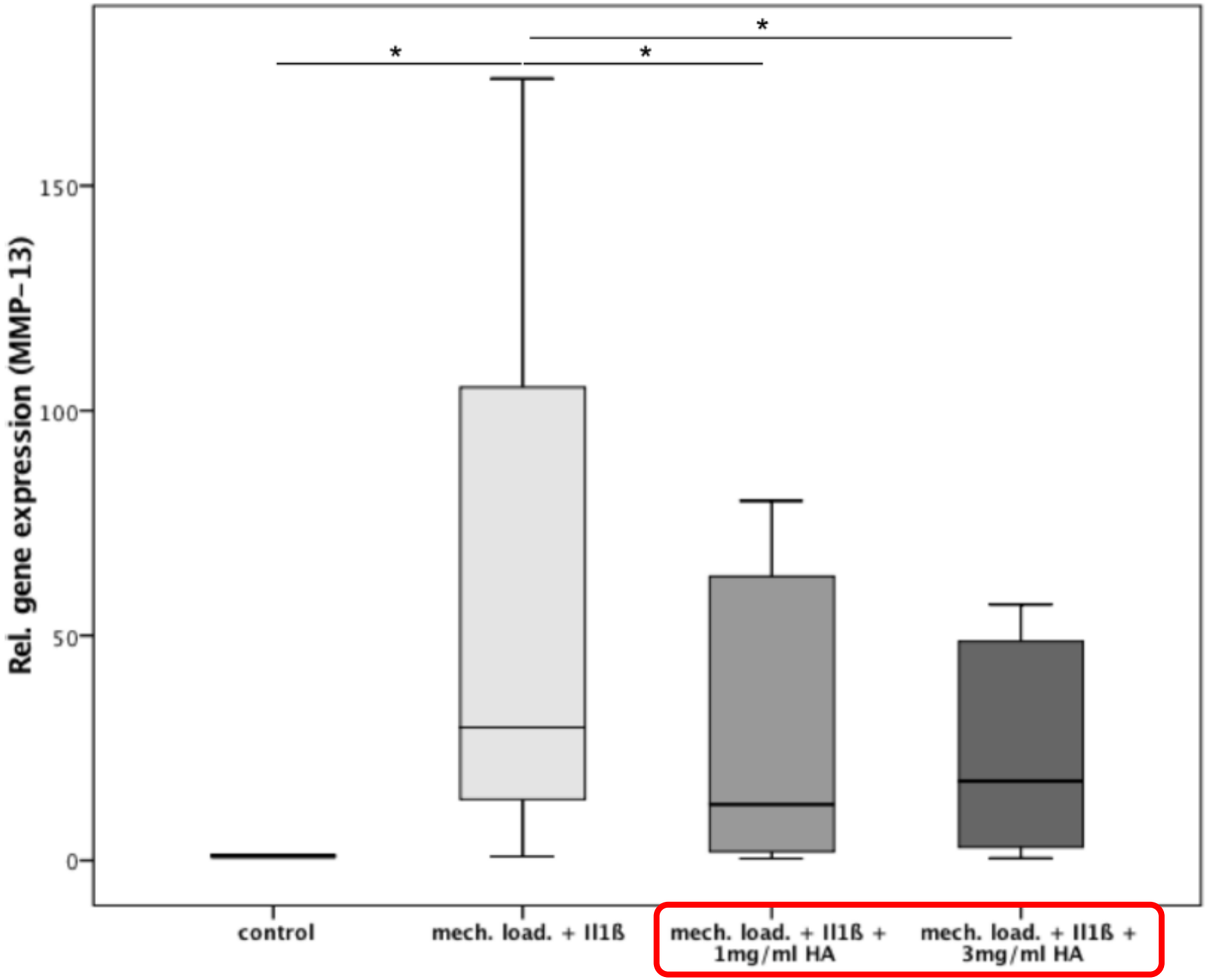


Fig 2. Relative gene expression of MMP-13 in the 3 study groups: (1) 2ng/ml IL1ß + mechanical loading, (2) 2ng/ml IL1ß + mechanical loading + 1mg/ml HA, (3) 2ng/ml IL1ß + mechanical loading + 3mg/ml HA and the control; * indicates statistical significance with $p<0,05$.

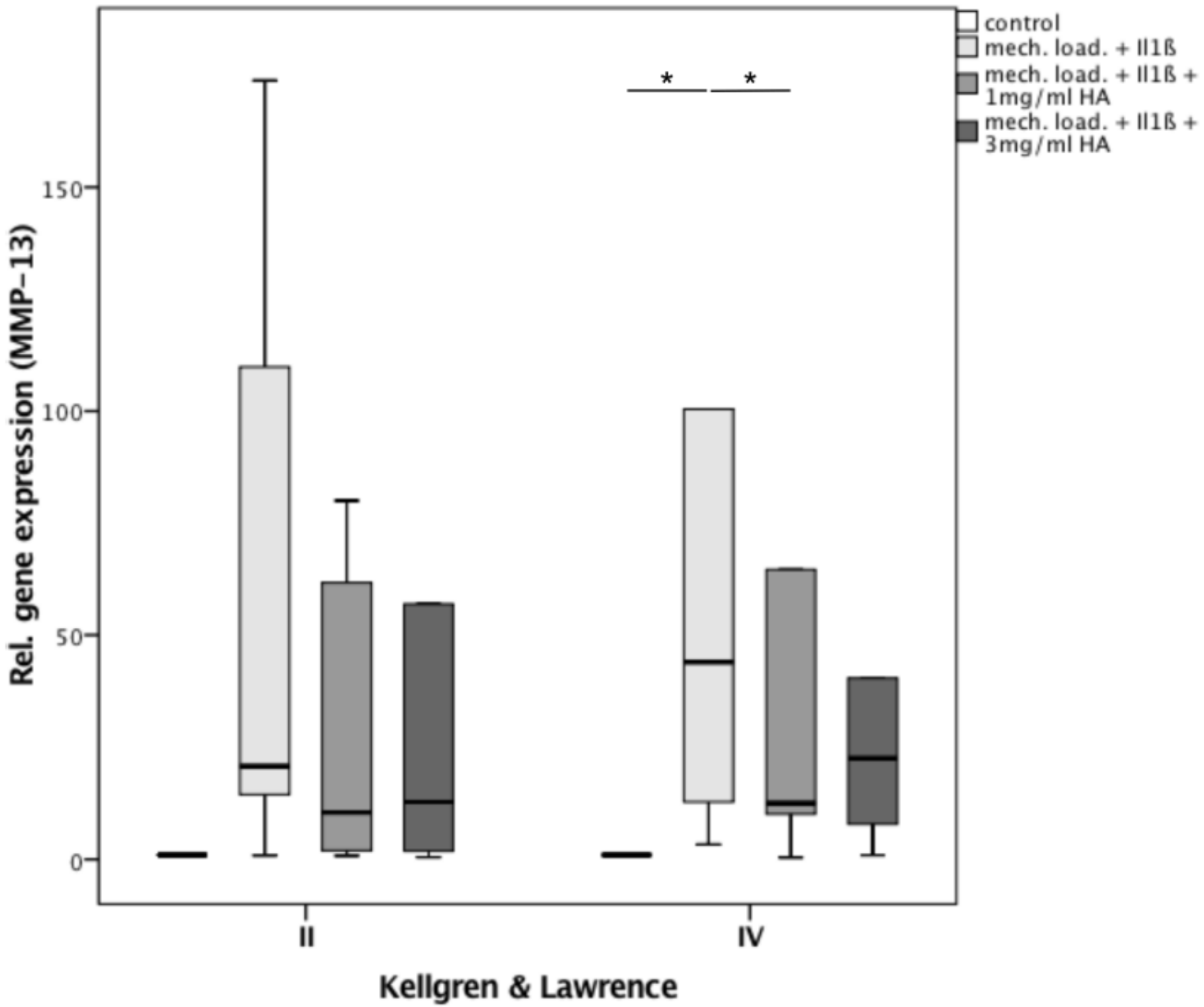


Fig 3. Separate analysis of relative gene expression of MMP-13 in all 3 study groups according to OA severity (K&L2 and K&L4): (1) 2ng/ml IL1ß + mechanical loading, (2) 2ng/ml IL1ß + mechanical loading + 1mg/ml HA, (3) 2ng/ml IL1ß + mechanical loading + 3mg/ml HA and the control; * indicates statistical significance with $p<0,05$.

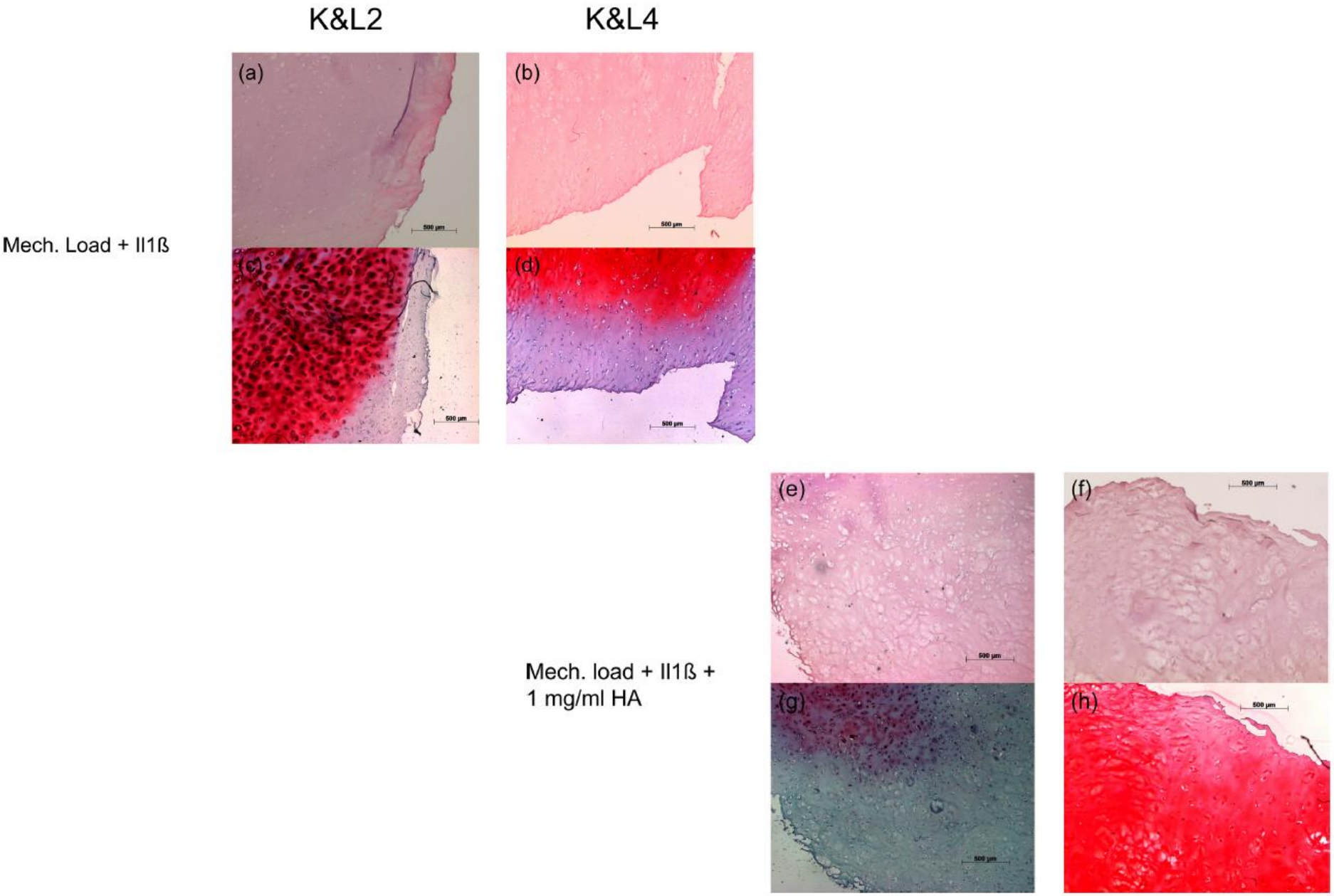
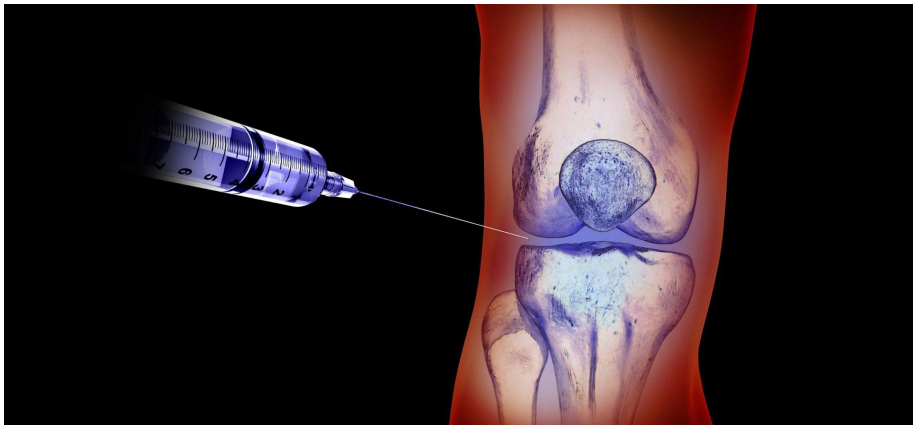


Fig 4. Photomicrographs of articular cartilage samples. (**a** and **b**) H&E stained sections of K&L2 and K&L4 cartilage samples upon stimulation with Il1ß and mechanical loading. (**c** and **d**) Safranin O stained sections of K&L2 and K&L4 cartilage samples upon stimulation with Il1ß and mechanical loading. (**e** and **f**) H&E stained sections of K&L2 and K&L4 cartilage samples upon additional administration of 1 mg/ml HA. (**g** and **h**) Safranin O sections of K&L2 and K&L4 cartilage samples upon additional administration of 1 mg/ml HA. Scale bar = 500 µm.

ALTRE TERAPIE INTRA-ARTICOLARI

- **CONCENTRATO PIASTRINICO AUTOLOGO**
- **CELLULE STAMINALI MESENCHIMALI AUTOLOGHE**
- **OZONO TERAPIA**
- **TOSSINA BOTULINICA**
- **FARMACI BIOTECNOLOGICI**
- **FGF 18 (fattore di crescita fibrobalstica – studi in fase 1)**



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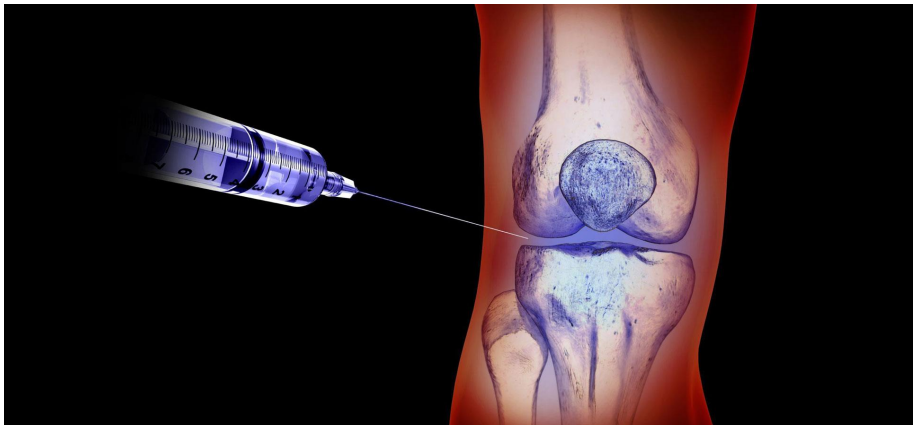
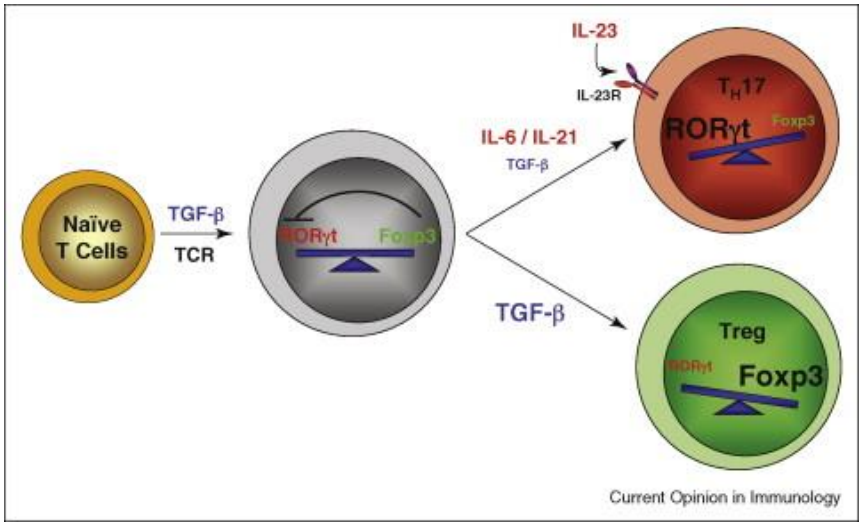
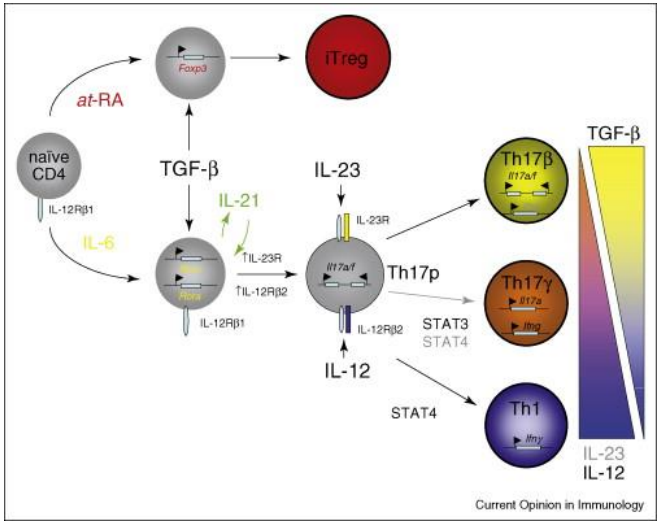


INIEZIONE DI CONCENTRATO PIASTRINICO - PRP

Razionale:

- Preparato ricco in Grow factors che incentivano i processi riparativi tissutali
- TGFbeta è associato a condrogensi nei processi di riparazione cartilaginea
- Aumenta la concentrazione di acido ialuronico





Sampson et al del 2010 Am .J. Phys Med Rehabil

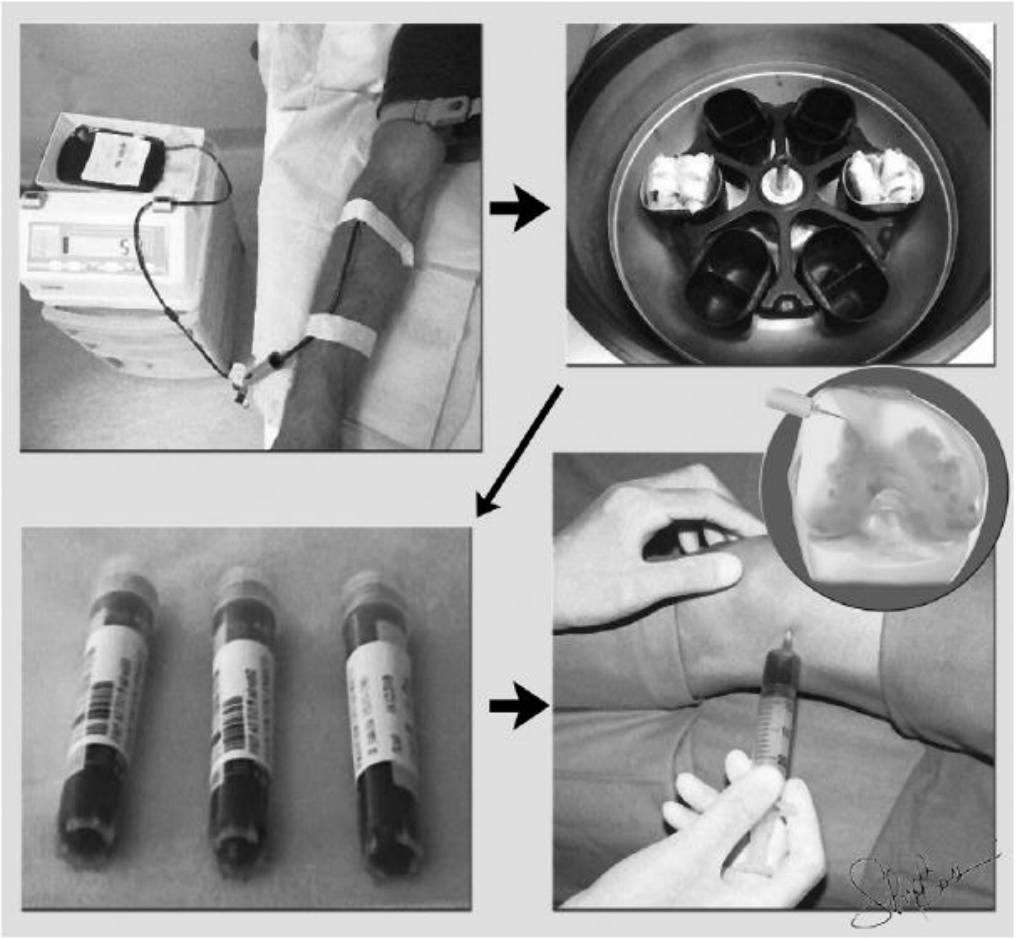
Preparziaone e metodica di somministrazione

Prelievo di 150 ml di sangue periferico per ginocchio.

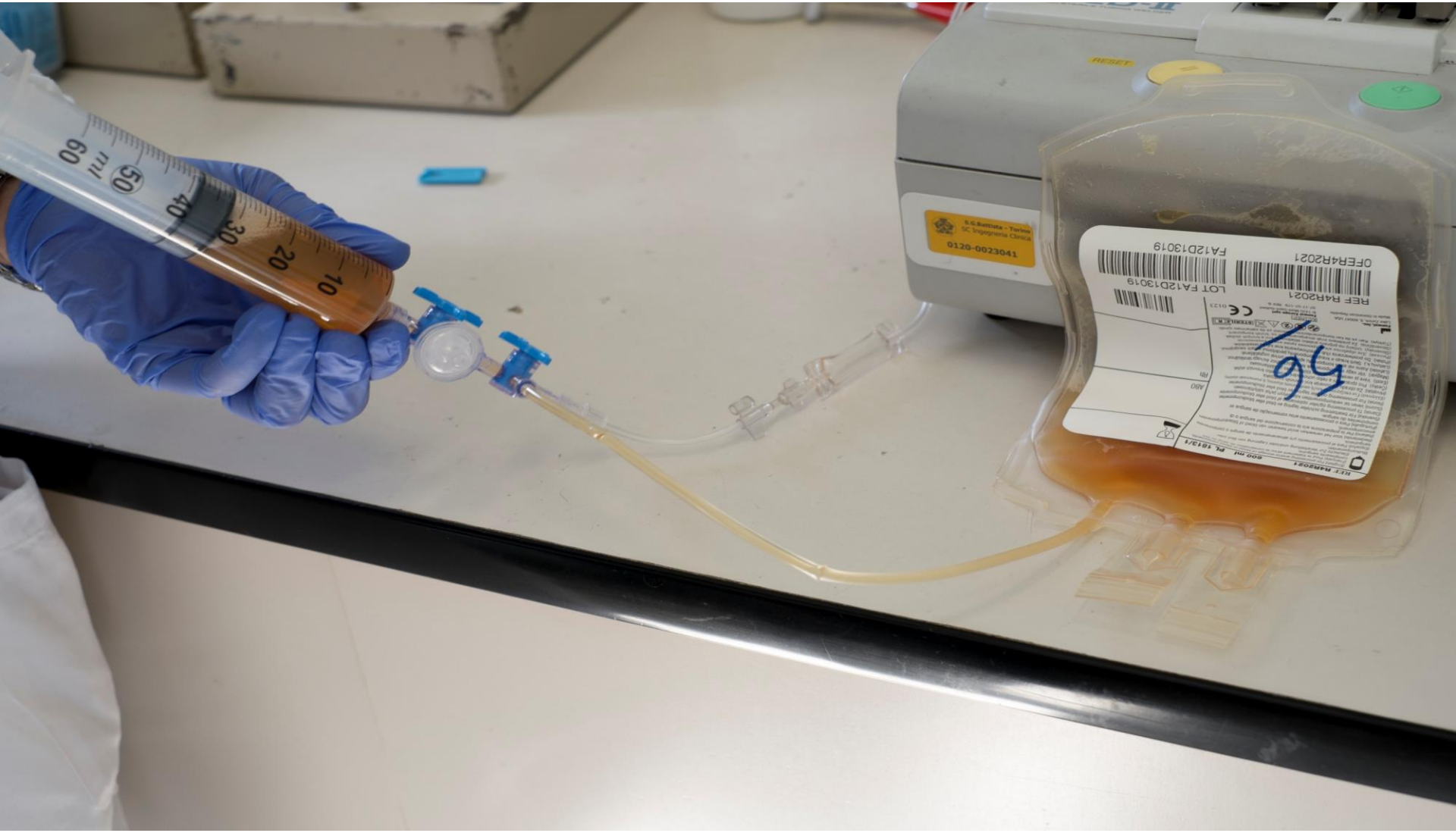
2 centrifugazioni:
Prima per separare gli eritrociti
(1480 rpm per 6 minuti)
Seconda per concentrare le PLT
(a 3400 rpmper 15 minuti)

20 ml di concentrato che viene diviso in 4 unità da 5 ml.Controllo per la qualità del concentrato (contenuto medio 6 bilioni di PLT)

Viene effettuate subito una prima infiltrazione poi conservate le altre unità per a -30 C° .
Seguita da altre due infiltrazioni ogni 14 gg.
Previo riscaldamento del preparato in termostato a 37 C° per 30 minuti



Arthroscopy: The Journal of Arthroscopic and Related Surgery, Vol 27, No 11 (November), 2011: pp 1490-1501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S.G.Battista - Torino
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20
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ml

Platelet-Rich Plasma Intra-Articular Injection Versus Hyaluronic Acid Viscosupplementation as Treatments for Cartilage Pathology: From Early Degeneration to Osteoarthritis

Elizaveta Kon, M.D., Bert Mandelbaum, M.D., Roberto Buda, M.D., Giuseppe Filardo, M.D., Marco Delcogliano, M.D., Antonio Timoncini, M.D., Pier Maria Fornasari, M.D., Sandro Giannini, M.D., and Maurilio Marcacci, M.D.

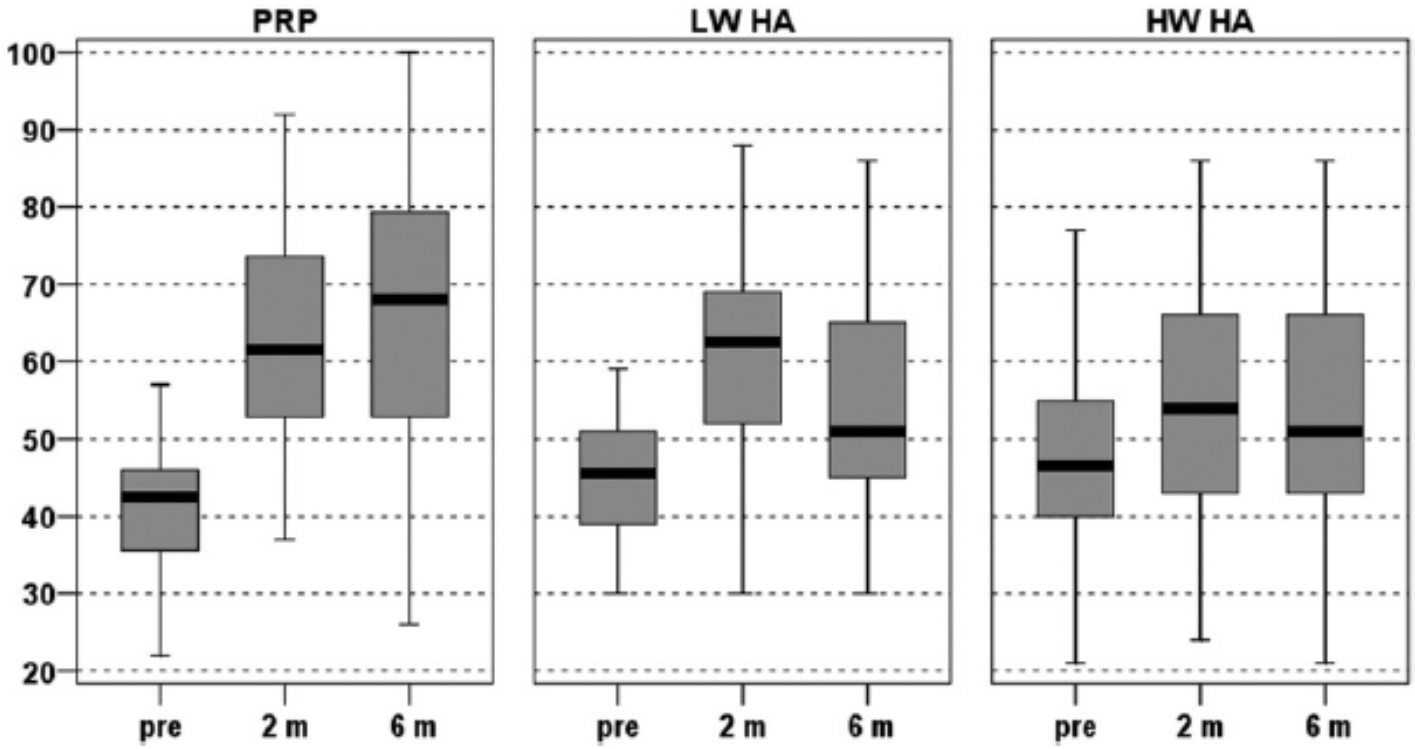
Arthroscopy: The Journal of Arthroscopic and Related Surgery, Vol 27, No 11 (November), 2011: pp 1490-1501

TABLE 1. *Comparison of Patient Characteristics of 3 Treatment Groups*

	PRP	LW HA	HW HA	
Age (yr)	50.6 ± 13.8 (30-81)	53.2 ± 13.0 (26-75)	54.9 ± 12.6 (29-76)	NS
Sex	30 M, 20 F	27 M, 23 F	25 M, 25 F	NS
Body mass index (kg/m^2)	24.6 ± 3.2 (18-32)	26.2 ± 2.2 (20-31)	24.8 ± 3.5 (20-35)	$P = .004$
Pathology				NS
Cartilage degeneration	22	19	21	
Early OA	20	22	19	
Advanced OA	8	9	10	
Previous surgery	18 (7 meniscectomies, 6 ACL, 1 PCL, 1 patellar osteosynthesis, 4 shavings, 1 microfracture, 1 mosaicplasty, 3 second-generation ACI)	13 (12 meniscectomies, 2 ACL, 1 tibial plateau fracture osteosynthesis, 5 shavings)	17 (7 meniscectomies, 9 ACL, 2 microfracture, 5 shavings)	NS

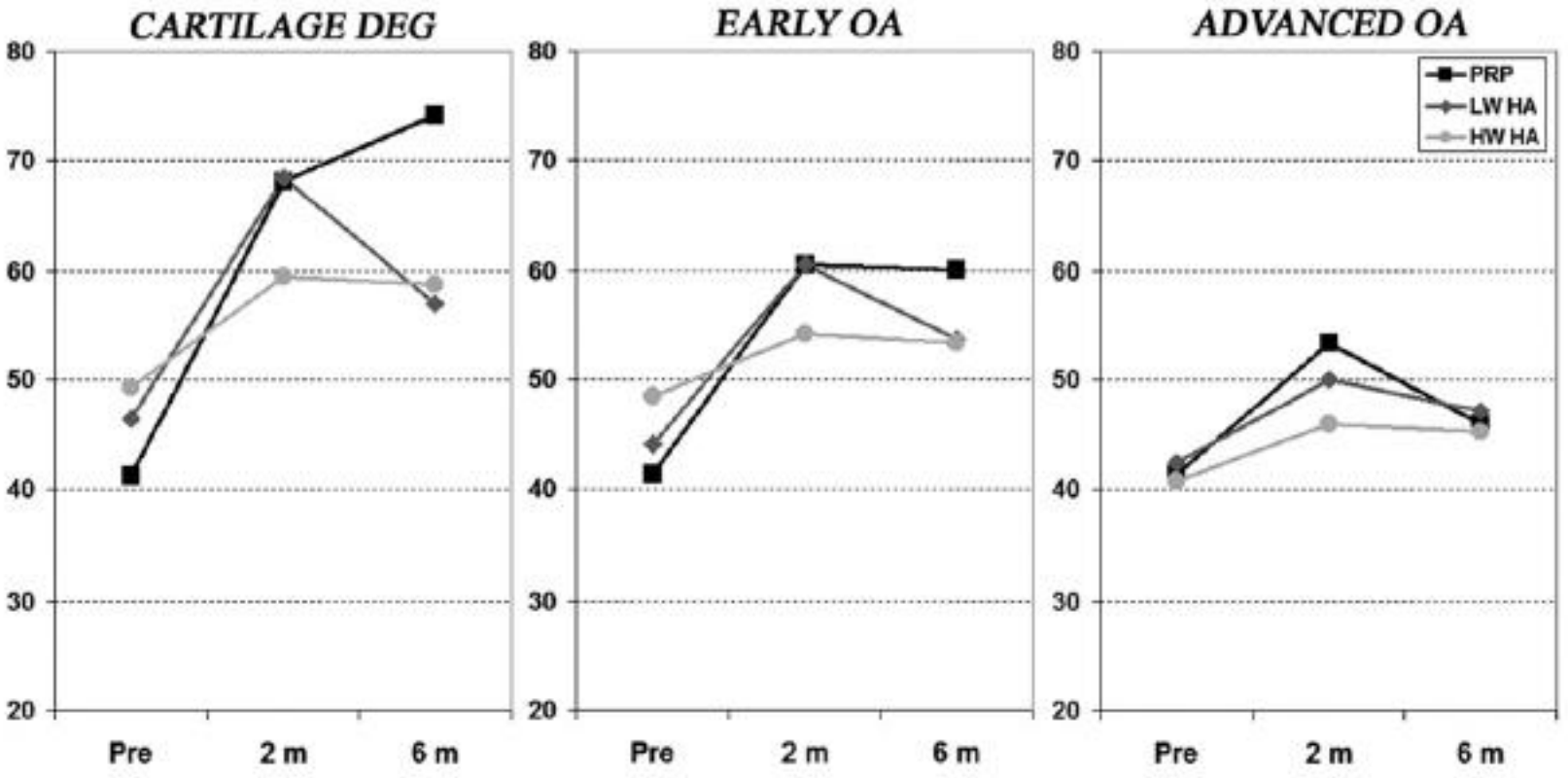
NOTE. The groups were homogeneous except for body mass index, which was higher in the LW HA group.
Abbreviations: ACI, autologous chondrocyte implantation; ACL, anterior cruciate ligament; PCL, posterior cruciate ligament.

IKDC score (0-100)



visits. Subjective International Knee Documentatior Committee (IKDC) and EQ VAS scores (as recom· mended by the International Cartilage Repair Society evaluation package) were used for clinical evaluation Adverse events and patient satisfaction were also re· corded.

IKDC score (0-100)



For this study, 150 consecutive patients affected by artilage degenerative lesions (Kellgren grade 0) (Fig), early OA (Kellgren grade I to III), and severe OA Kellgren grade IV) were enrolled and treated with

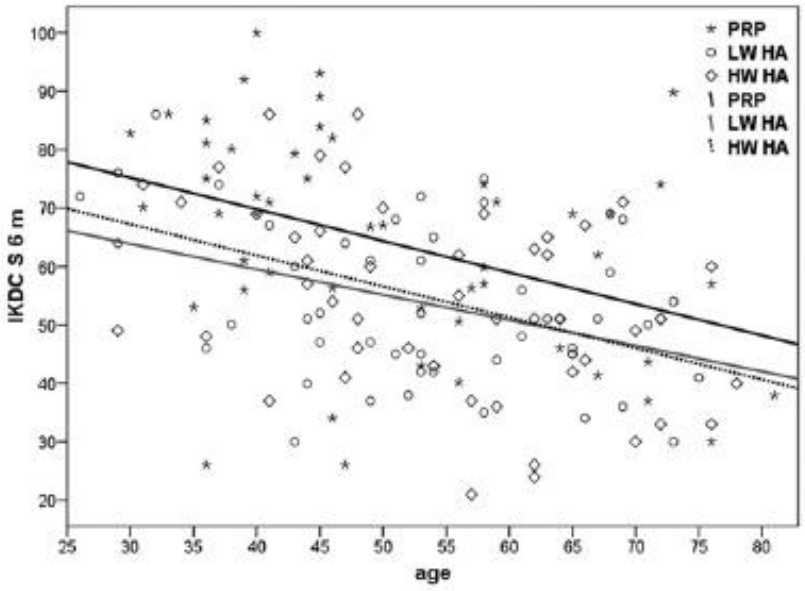


FIGURE 5. In all treatment groups age was correlated with the clinical outcome: at 6 months of follow-up (6 m), older patients obtained the worst IKDC subjective (S) results.

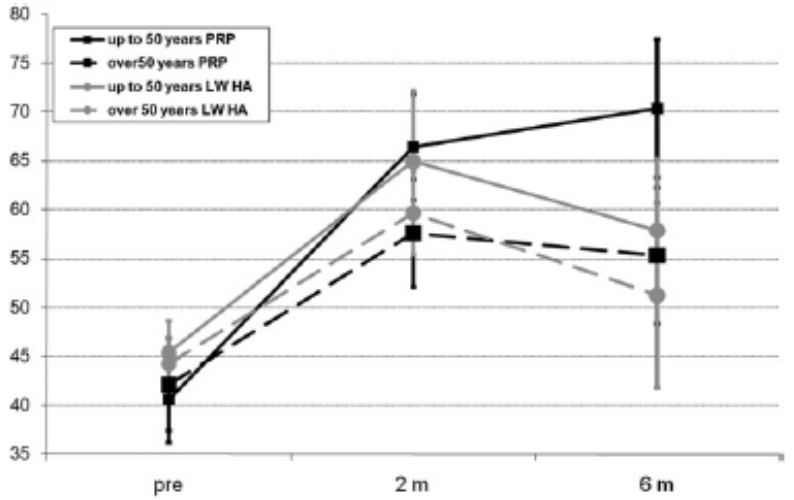


FIGURE 8. Age-related results showing IKDC subjective evaluation of 2 subgroups analyzed: patients aged 50 years or younger and patients aged over 50 years. In younger patients PRP was more effective at 6 months, whereas in older patients results were equivalent at both 2 months (2 m) and 6 months (6 m). (pre, pretreatment.)

CONCLUSIONS

The clinical results of this comparative study suggest that this procedure may be useful for the treatment of degenerative articular pathology of the knee. Autologous PRP injections showed more and longer efficacy than HA injections in reducing pain and symptoms and recovering articular function, in particular in more active patients with a low degree of cartilage degeneration. In patients aged 50 years or younger, LW HA and PRP were more effective than HW HA at 2 months and PRP was more effective than LW HA or HW HA at 6 months, whereas in patients older than 50 years, results were equivalent at both 2 and 6 months.

Drug Design, Development and Therapy

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ORIGINAL RESEARCH

Intra-articular platelet-rich plasma versus hyaluronic acid in the treatment of knee osteoarthritis: a meta-analysis

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy

Table 1 Detailed information of the included studies

Reference	Group	Age (years)	Gender (M/F)	OA type (C/E/A)	BMI (kg/m^2)	Intervention	Follow-up (months)
Kon et al, 2011[9]	PRP	50.6±13.8	30/20	C22; E20; A8	24.6±3.2	3 times, 5 mL, every 2 weeks	2, 6
	HWHA	54.9±12.6	25/25	C21; E19; A10	24.8±3.5	30 mg/2 mL, 1,000 to 2,900 kDa	
	LWHA	53.2±13.0	27/23	C19; E22; A9	26.2±2.2	20 mg/2 mL, 500 to 730 kDa	
Cerza et al,[26] 2012	PRP	66.5±11.3	25/35	E 21/24/15	N	4 times, 5.5 mL, weekly	1, 2, 6
	HA	66.2±10.6	28/32	E 25/22/13	N	4 times, 20 mg/2 mL	
Sanchez et al,[20] 2012	PRP	60.5±7.9	43/46	E 45/32/12	27.9±2.9	3 times, 8 mL, weekly	1, 2, 6
	HA	58.9±8.2	42/45	E 42/32/11	28.2±2.7	3 times	
Spakova et al,[25] 2012	PRP	52.8±12.4	33/27	E 2/39/19	27.9±4.1	3 times, 3 mL, weekly	3, 6
	HA	53.2±14.5	31/29	E 2/37/21	28.3±4.0	3 times	
Say et al,[24] 2013	PRP	55.2±7.8	5/40	E 1/17/27	32.4±4.0	1 time	3, 6
	LWHA	56.2±5.1	6/39	E 1/15/29	32.3±3.3	3 times, 25 mg/2.5 mL, 730 to 900 kDa, weekly	
Vaquerizo et al,[27] 2013	PRP	62.4±6.6	16/32	E 0/14/26; A8	30.7±3.6	3 times, 8 mL, every 2 weeks	6, 12
	HWHA	64.8±7.7	22/26	E 0/18/21; A9	31.0±4.6	1 time, 60 mg/3 mL	
Filardo et al,[28] 2015	PRP	53.3±13.2	60/34	E 2.0±1.1	26.6±4.0	3 times, 5 mL, weekly	2, 6, 12
	HWHA	57.6±11.8	52/37	E 2.0±1.1	26.9±4.4	3 times, 20 mg/2 mL, >1,500 kDa, weekly	
Gormeli et al,[29] 2017	PRP*	53.7±13.1	23/16	E 26; A13	28.7±4.8	3 times, 5 mL, weekly	6
	PRP#	53.8±13.4	25/19	E 25; A14	28.4±4.4	1 time, 5 mL	
	HA	53.5±14	22/17	E 27; A13	29.7±3.7	3 times, 20 mg/2 mL, weekly	
Raeissadat et al,[30] 2015	PRP	56.9±9.1	8/69	E6/44/38; A12	28.2±4.6	2 times, 5 mL, monthly	1, 6, 12
	LWHA	61.1±7.5	15/47	E0/47/37; A16	27.0±4.2	3 times, 20 mg/2 mL, 500 to 730 kDa, monthly	
Lana et al,[31] 2016	PRP	60.9±7	7/29	E 9/14/13	27.4±6.9	1 time, 5 mL	1, 3, 6, 12
	HWHA	60±6.6	3/33	E 9/16/11	28.2±8.8	20 mg/2 mL, 2,400 to 3,600 kDa	
	P&A	62±6.1	6/27	E 5/14/14	29.2±7.3	5 mL+2 mL	
Duymus et al,[32] 2017	PRP	60.4±5.1	1/32	E 0/22/11	27.6±4.6	2 times, 5 mL per time, every 2 weeks	1, 3, 6, 12
	HWHA	60.3±9.1	1/33	E 0/24/10	28.4±3.6	40 mg/2 mL, 1,600 kDa	
Montanez-Heredia et al,[33] 2016	PRP	66.3±8.3	12/15	E 5/10/12	29.0±5.5	3 times, every 2 weeks	3, 6
	LWHA	61.5±8.6	9/17	E 2/9/15	30.4±4.9	3 times, 25 mg/2.5 mL, 799 kDa	
Cole et al,[21] 2017	PRP	55.9±10.4	28/21	E 3/2620	27.4±3.9	3 times, 4 mL, weekly	3, 6, 12
	LWHA	56.8±10.5	20/30	E 1/27/22	29.0±6.4	3 times, 16 mg/2 mL, 6,000 kDa	

Notes: *Three injections of PRP; #one injection of PRP. OA type (C/E/A): chondropathy, Kellgren grade 0/early, Kellgren grade I to III/advanced, Kellgren grade IV.
Abbreviations: OA, osteoarthritis; BMI, body mass index; PRP, platelet-rich plasma; HA, hyaluronic acid; HWHA, high-molecular weight hyaluronic acid; LWHA, low-molecular weight hyaluronic acid; P&A, PRP and HA.

Drug Design, Development and Therapy

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ORIGINAL RESEARCH

Intra-articular platelet-rich plasma versus hyaluronic acid in the treatment of knee osteoarthritis: a meta-analysis

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy

Conclusion

PRP injections reduced pain more effectively than HA injections in OA of the knee at 6 and 12 months of follow-up evaluated by WOMAC pain score, while the VAS showed no significant difference at 3 and 6 months. Additionally, similar results were observed for the function recovery according to the WOMAC function score and EQ VAS. Due to the limited quality and data of the evidence currently available, more high-quality randomized controlled trials are required.

Clinical Rheumatology
https://doi.org/10.1007/s10067-018-3985-6

ORIGINAL ARTICLE

Comparison of hyaluronic acid and PRP intra-articular injection with combined intra-articular and intraosseous PRP injections to treat patients with knee osteoarthritis

Ke Su[1] · Yuming Bai[1] · Jun Wang[1] · Haisen Zhang[1] · Hao Liu[2] · Shiyun Ma[1]

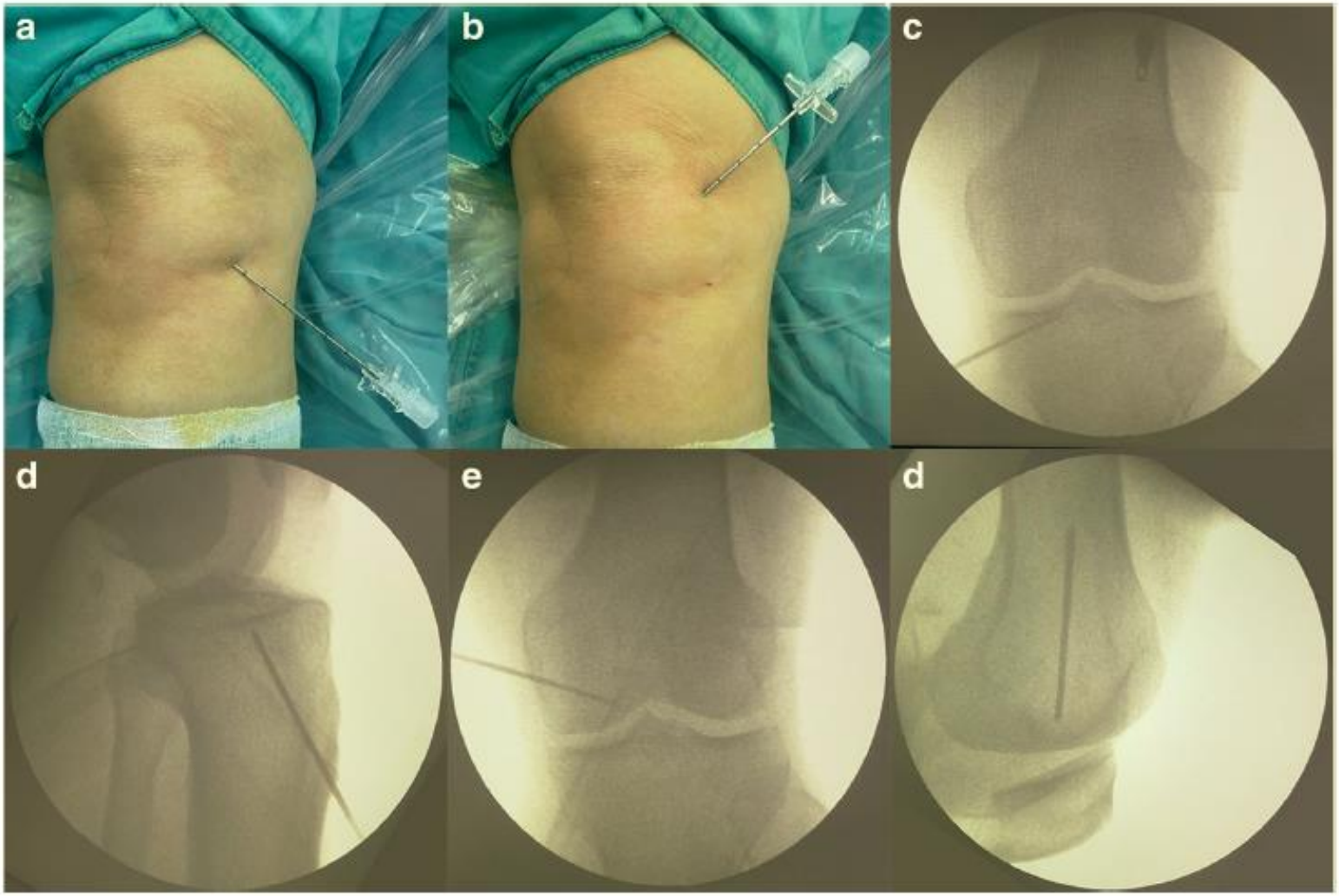

Fig. 2 A patient is positioned supine for intraosseous injection with C-arm guidance. **a**, **b** Intraosseous injection at the medial aspect of the tibial plateau and femoral condyle located 1 cm proximal and 1 cm distal to the medial joint line at an angle of 30–40° to the lower limb anatomical axis. **c**, **d** Trocar tip is located at the medial aspect of the tibial intercondylar eminence in the anteroposterior view and the midpoint of the anteroposterior diameter of the tibial plateau in the lateral view. **e**, **f** Trocar tip is located at the midpoint of the femoral trochlea in the anteroposterior view and the midpoint of the anteroposterior diameter of the femoral condyle in the lateral view

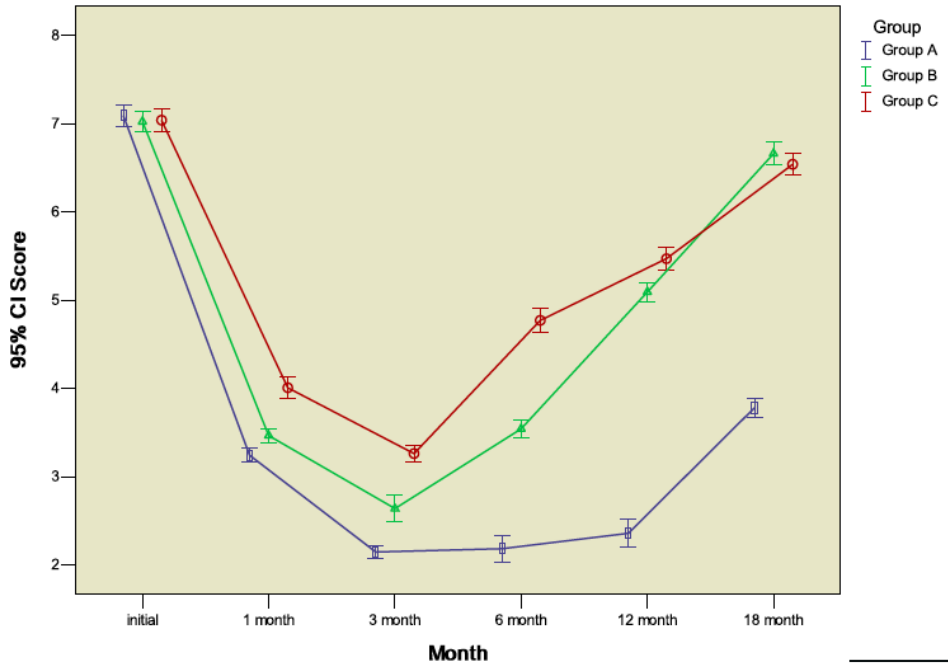

Fig. 3 VAS pain scores, comparison between the three groups (0–10)

Conclusion

Our study provides some evidence that the combination of intraosseous with intra-articular injection of PRP improves self-reported pain and subscales of WOMAC in patients with knee OA (Kellgren-Lawrence grade II to III); moreover, it is superior to the intra-articular injection of PRP or HA at 18 months at minimum and an encouraging treatment option.

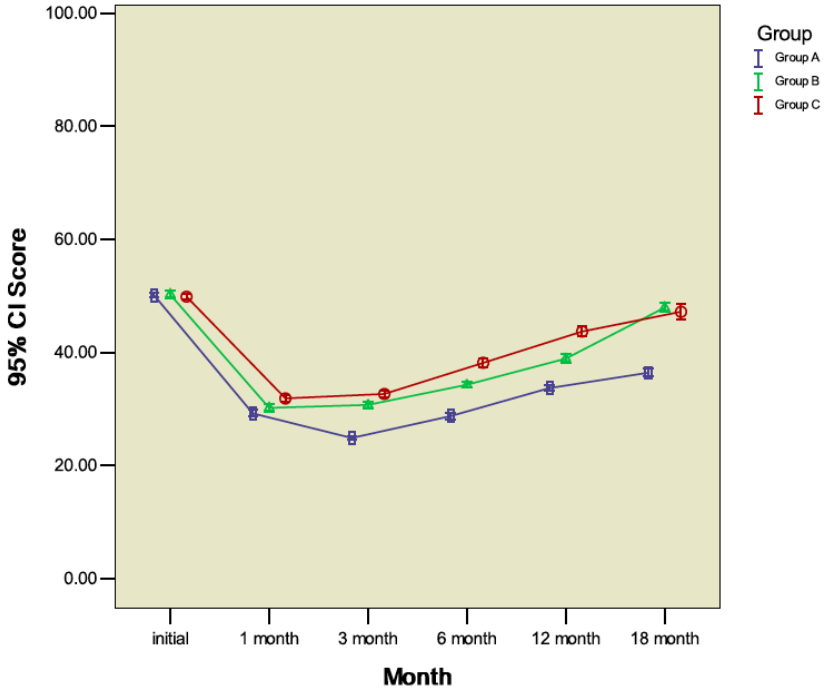

Fig. 4 Total WOMAC scores, comparison between the three groups (0–96)

ALTRE TERAPIE INTRA-ARTICOLARI

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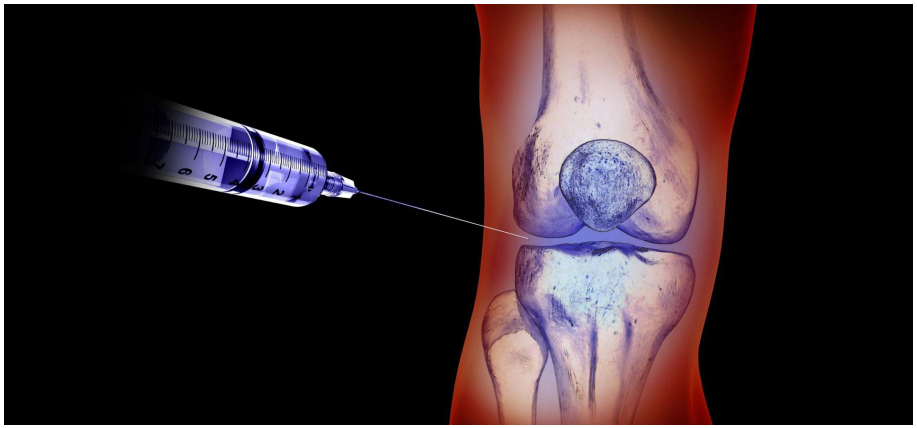
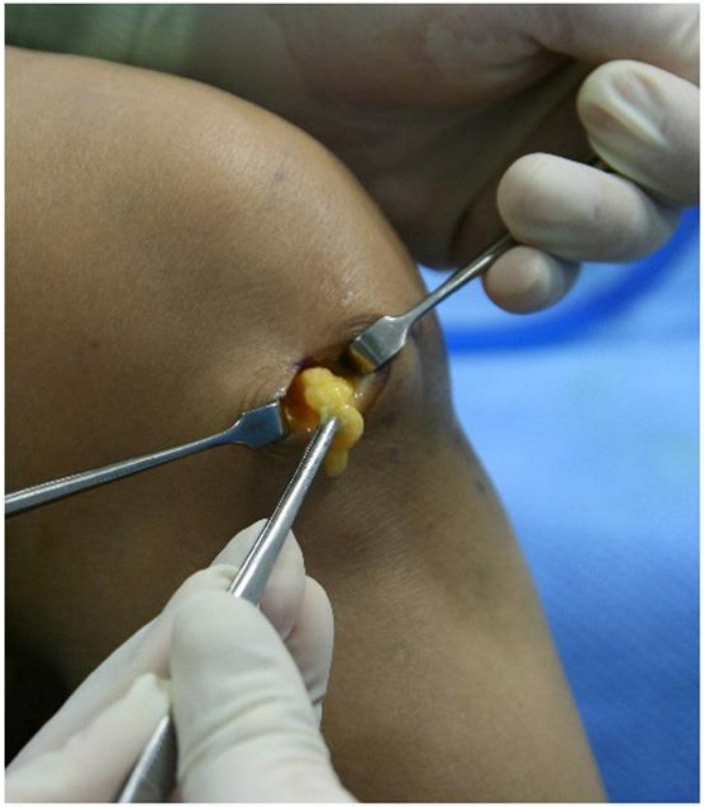
- FARMACI BIOTECNOLOGICI
- FGF 18 (fattore di crescita fibrobalstica –studi in fase 1)



CELLULE STAMINALI MESENCHIMALI AUTOLOGHE

Trattamento artroscopico del ginocchio affetto: sinoviectomia, pulizia a seguito prelievo del grasso sinoviale infra-patellare da cui si ottengono le cellule staminali mesenchimali che vengono preparate con circa 3ml di PRP iniettate in articolazione a circa 3-4 ore da precedente intervento



Infrapatellar fat pad-derived mesenchymal stem cell therapy for knee osteoarthritis

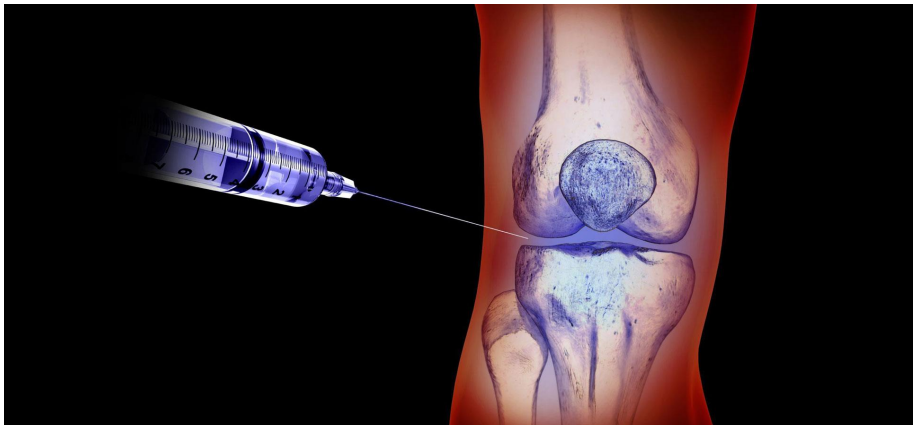
Yong-Gon Koh, Yun-Jin Choi *

The Knee 19 (2012) 902–907

Ancora scarsi dati sull'uomo a partire dal 2011
4 pazienti Davatchi F et al. Int Rheum Dis 2011
6 pazienti Emaldedin M ,et al .Arch Iran Med 2012

ALTRE TERAPIE INTRA-ARTICOLARI

- CONCENTRATO PIASTRINICO AUTOLOGO
- CELLULE STAMINALI MESENCHIMALI AUTOLOGHE
- **OZONO TERAPIA**
- TOSSINA BOTULINICA
- FARMACI BIOTECNOLOGICI
- FGF 18 (fattore di crescita fibrobalstica –studi in fase 1)



Accepted Manuscript

Intra-articular oxygen-ozone versus hyaluronic acid in knee osteoarthritis: A meta-analysis of randomized controlled trials

Qingsong Li, Xin Qi, Zhenxiang Zhang

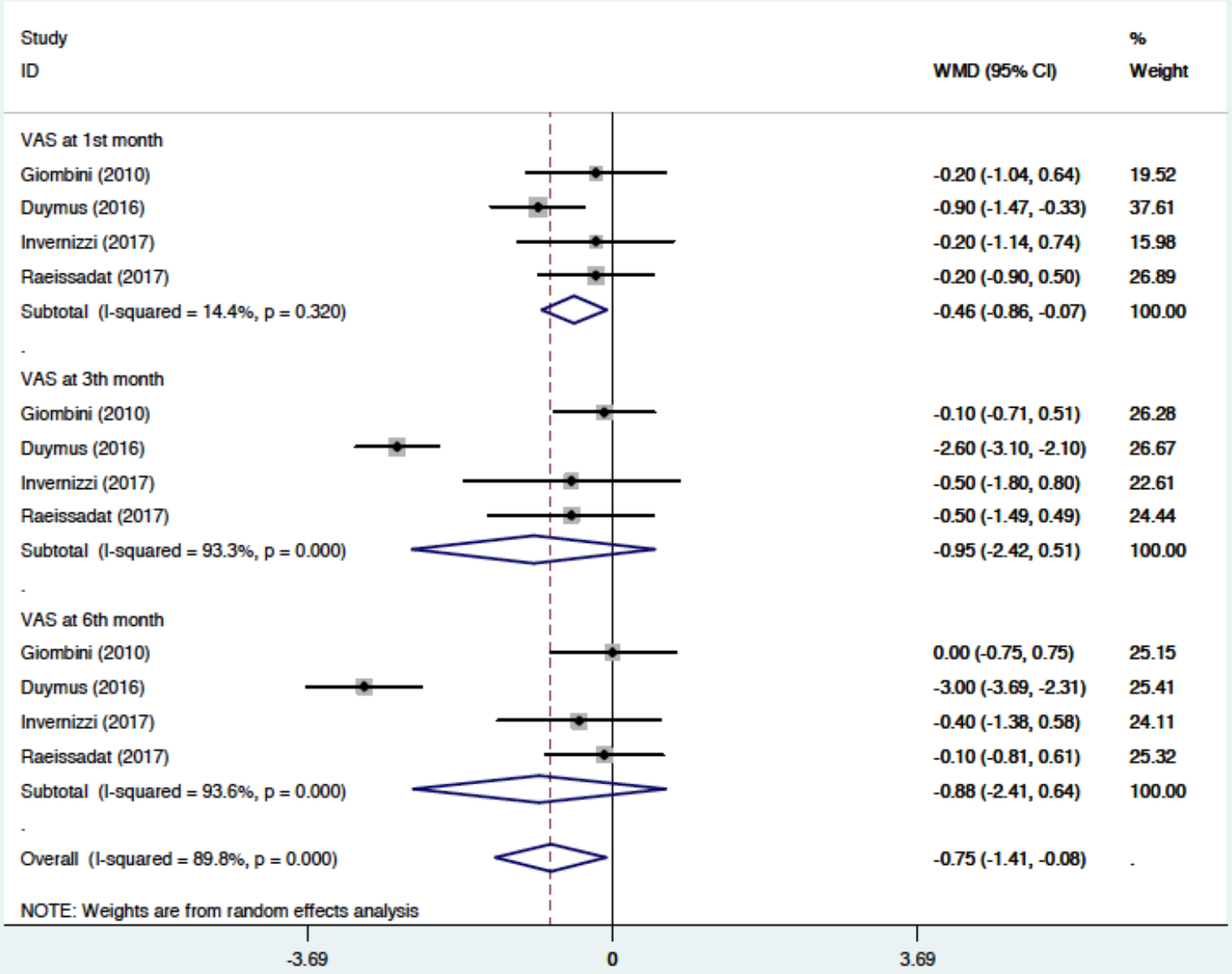


Fig. 2 Forest plot diagram showing VAS score

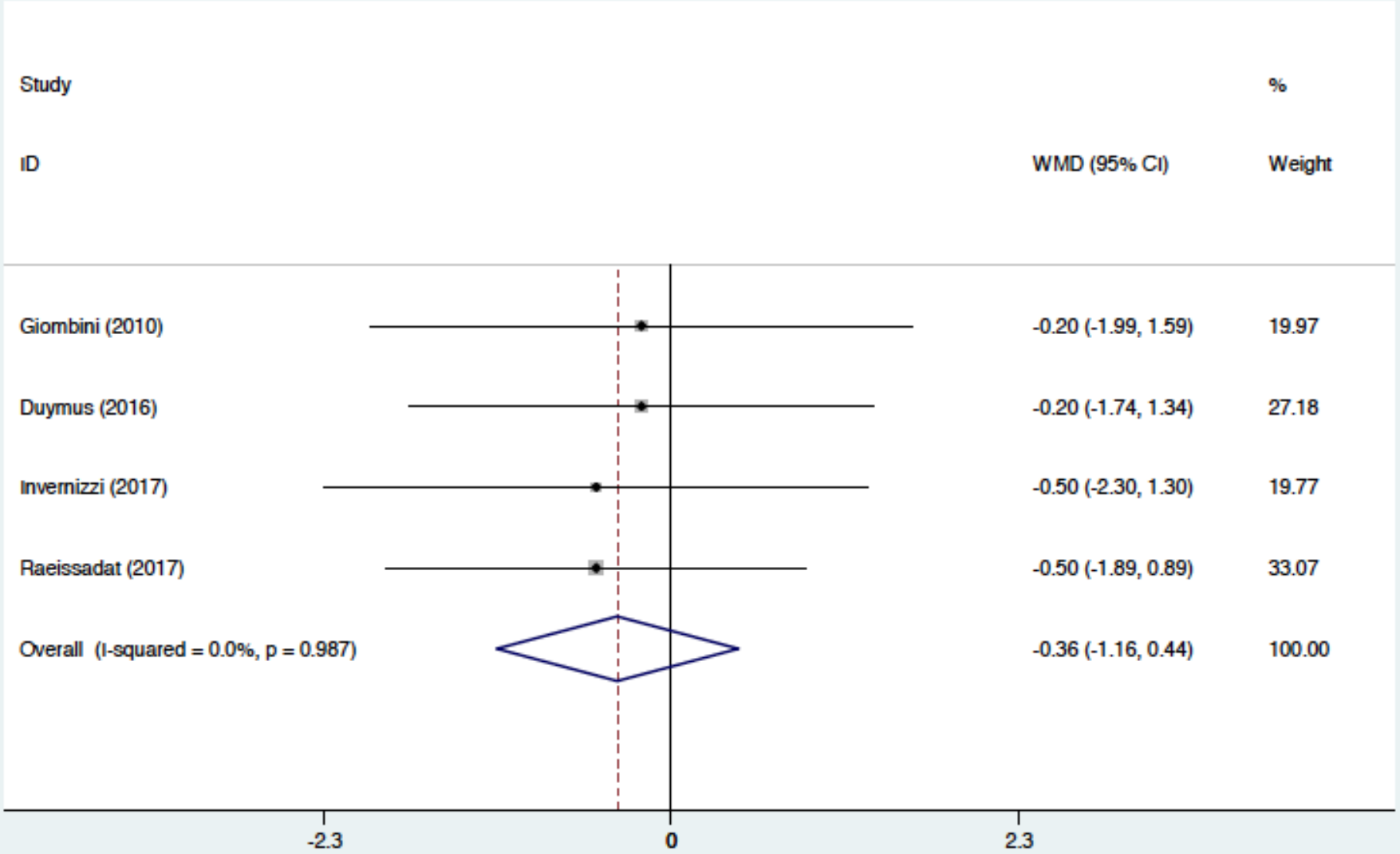


Fig. 3 Forest plot diagram showing WOMAC pain

TERAPIA INFILTRATIVA

TERAPIA INFILTRATIVA

CONTROINDICAZIONI

- Infezione articolare o periarticolare
- Versamento
- Eritema nella zona da infiltrare
- Allergie conosciute ai prodotti somministrati
- Pazienti in trattamento con anticoagulante orale per possibile emartro/ematoma legato alla manovra

TERAPIA INFILTRATIVA

EFFETTI COLLATERALI

- Manifestazioni allergiche locali in sede di iniezione (arrossamento cutaneo, reazione orticarioide)
- Manifestazioni generali-sistemiche con disturbi respiratori (reazione vagale alla iniezione)
- Infezione articolare cutanea
- Sinoviti

TERAPIA INFILTRATIVA

OTTIMIZZAZIONE DELLA TECNICA DI ESECUZIONE

- Attenzione
- Precisione
- Rigore
- Conoscenza dell’anatomia
- Certezza che il farmaco raggiunga localmente la sede interessata

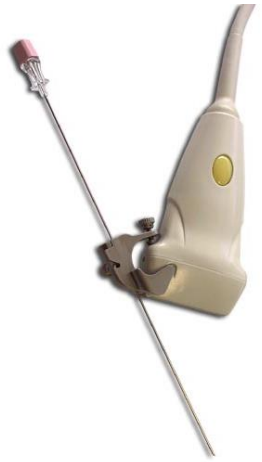
TERAPIA INFILTRATIVA

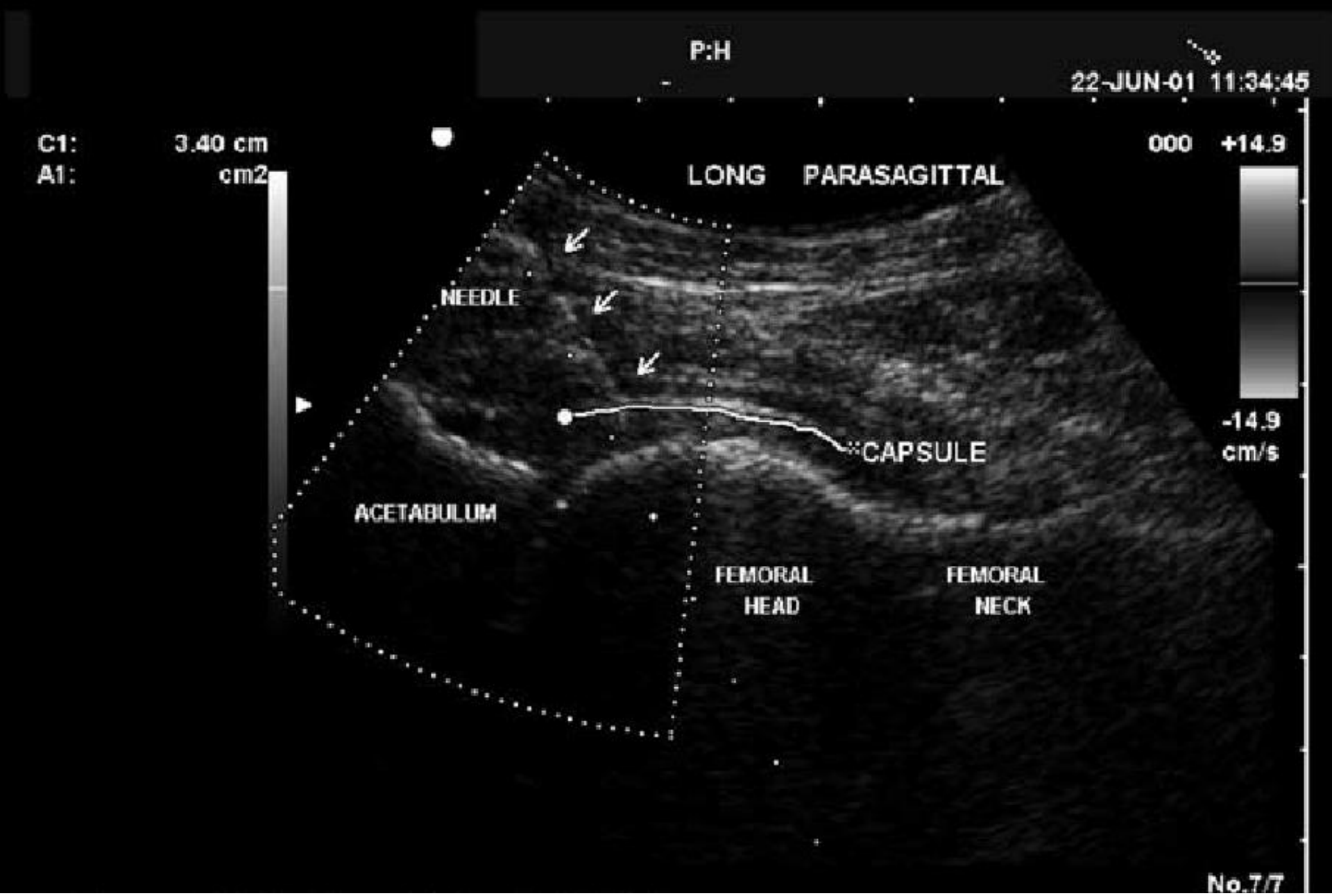
IMAGING

- Guida Fluoroscopica
- Guida TC
- Guida Ecografica

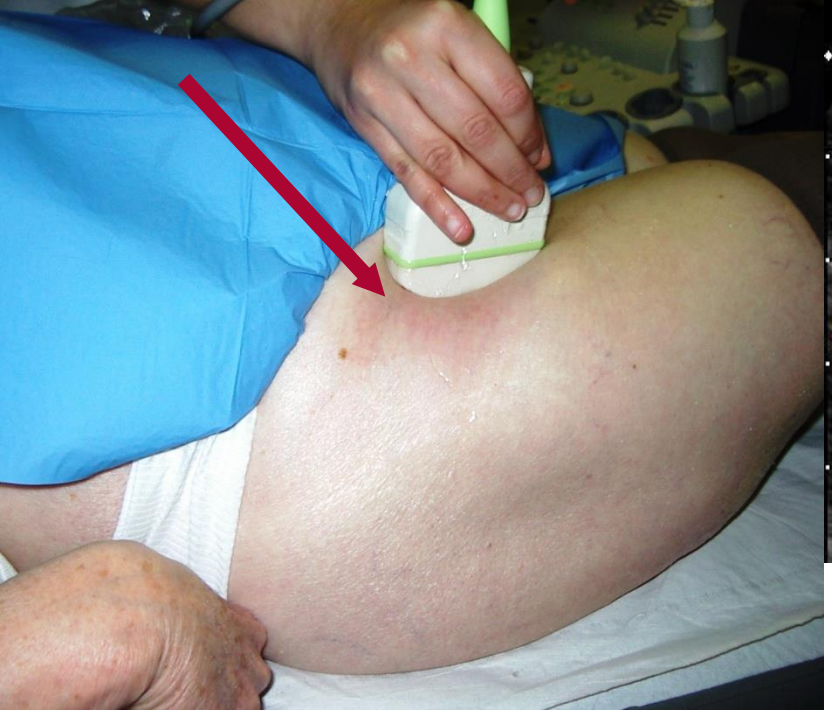
TERAPIA INFILTRATIVA

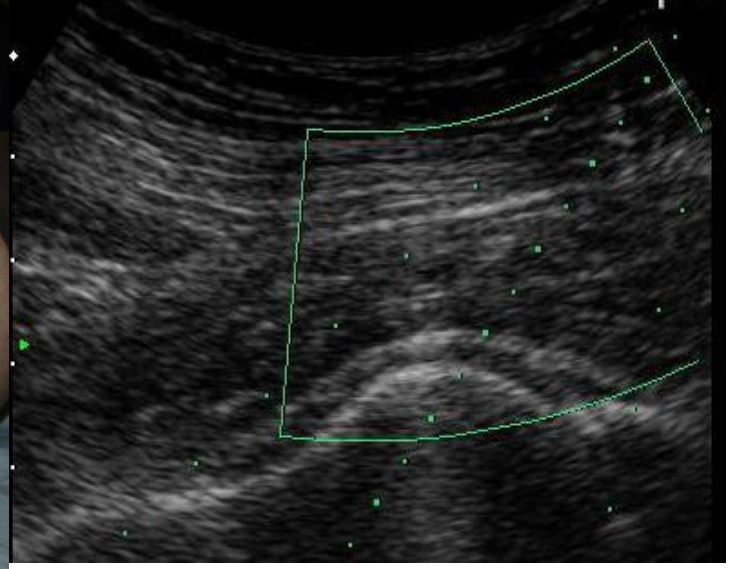
Guida Ecografica





Migliore et al. OsteoArthritis and Cartilage 2003

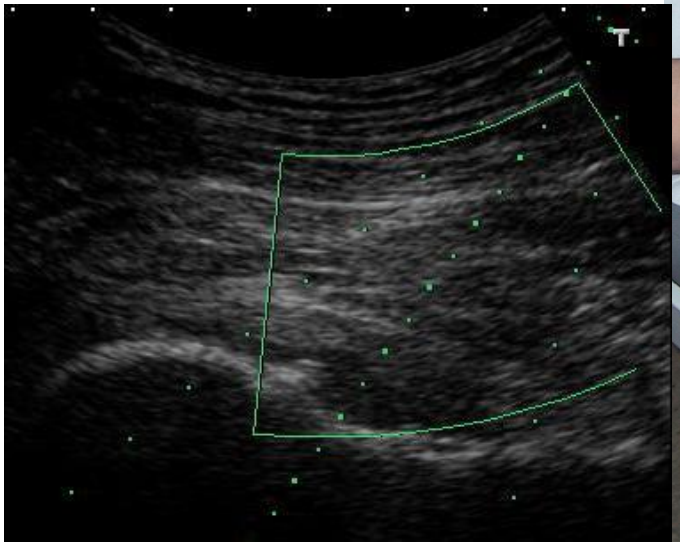


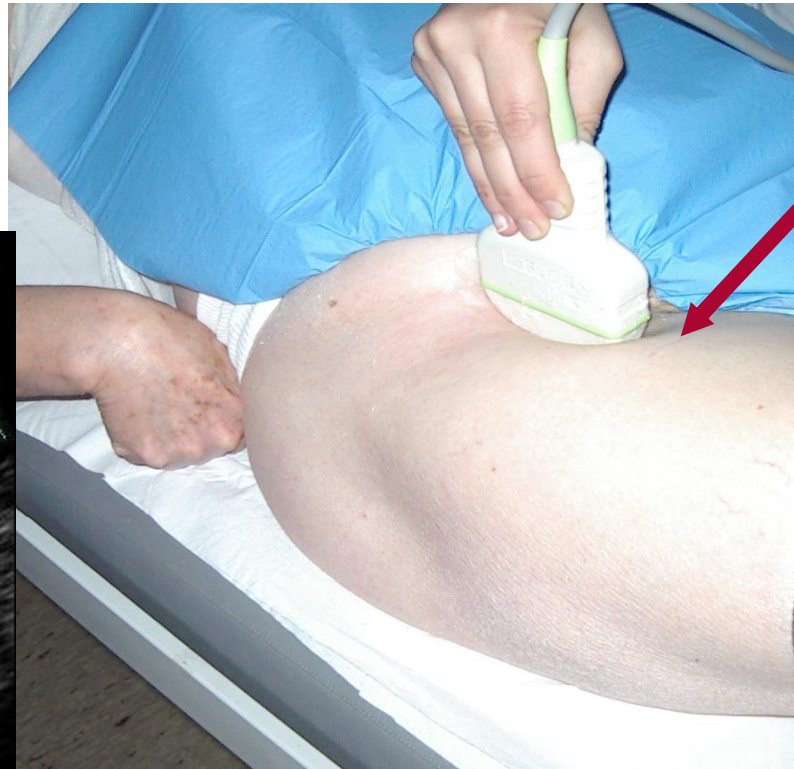


Accesso parasagittale antero-superiore

Guida ecografica diretta

Accesso parasagittale antero-inferiore

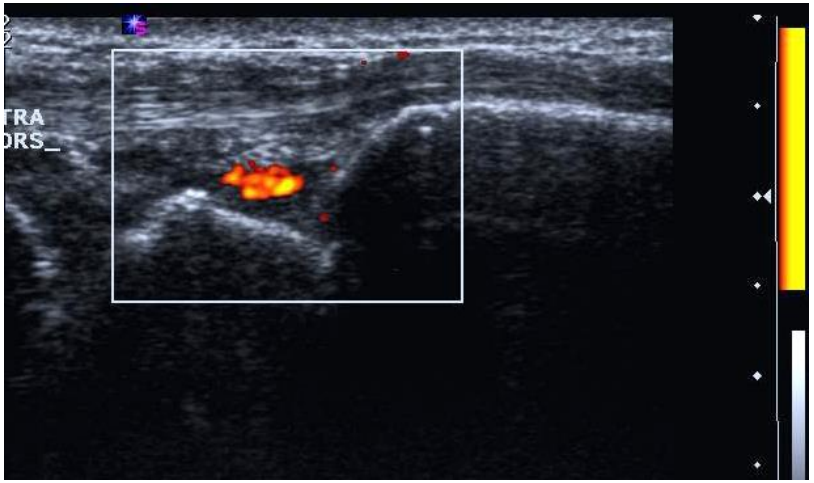


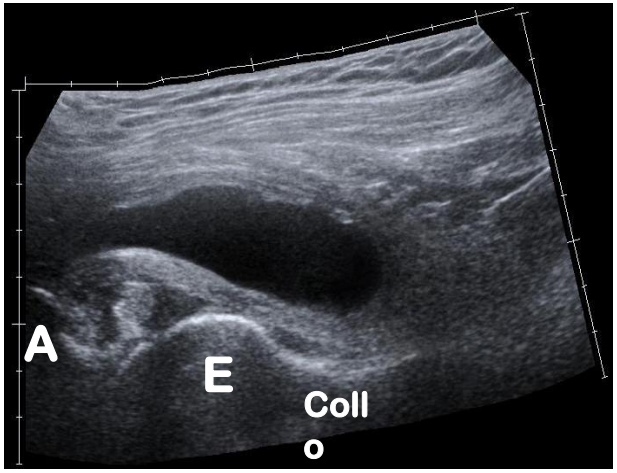


TERAPIA INFILTRATIVA

UTILITA' DELL' ECOGRAFIA

Consente di valutare le strutture muscolari, tendinee, capsulari, le borse, l'impegno sinoviale (versamento – proliferazione sinoviale) e con l'impiego del power-Doppler l'iperemia, espressione dell'attività infiammatoria della sinovia.





AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

S.C.
Reumatologia
AO
Città della Salute
e della Scienza
di Torino

ULTRASONOGRAHPIC EVALUATION OF HYALURONIC ACID EFFECTIVENESS IN THE TREATMENT OF GONARTHROSIS WITH SYNOVIAL INVOLVMENT

RHEUMATOLOGY

Rheumatology 2013;52:1425–1428
doi:10.1093/rheumatology/ket136
Advance Access publication 9 April 2013

Concise report

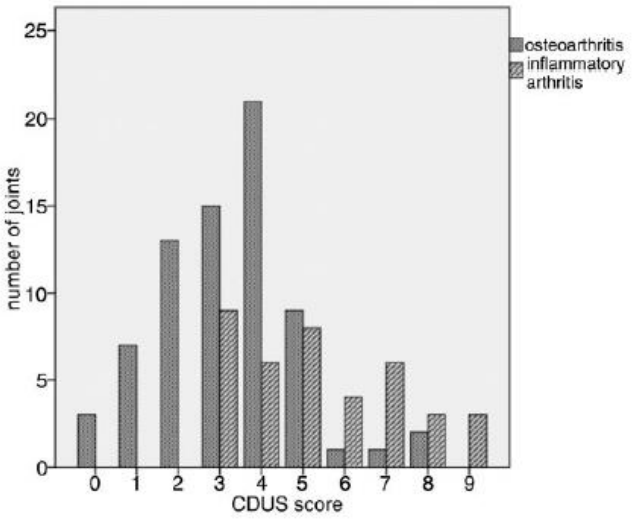
The value of colour Doppler sonography of the knee joint: a useful tool to discriminate inflammatory from non-inflammatory disease?

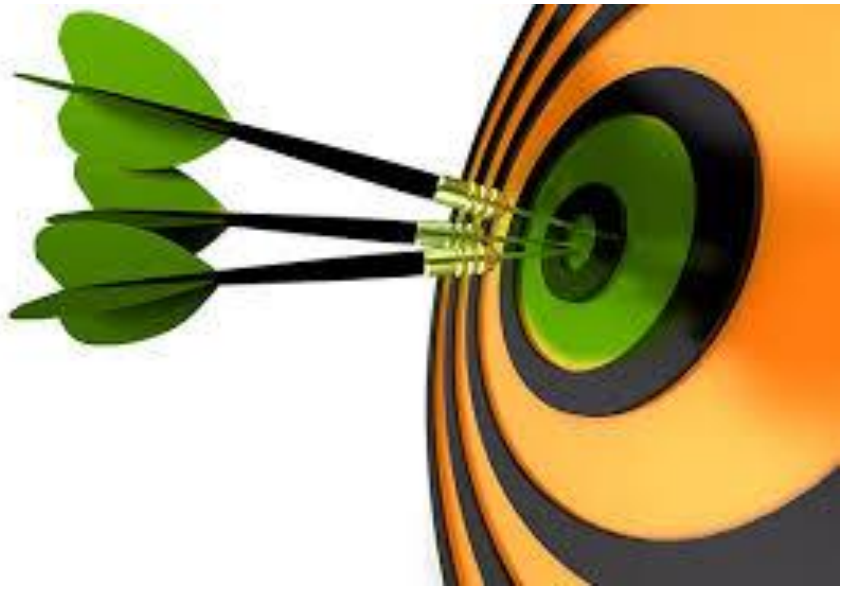
Nelly Beitinger[1], Boris Ehrenstein[1], Benno Schreiner[2], Martin Fleck[1], Joachim Grifka[2], Christian Lüring[3] and Wolfgang Hartung[1]

Rheumatology key messages

- PDUS is a useful tool to distinguish inflammatory from non-inflammatory knee swelling.
- There is no definitive PDUS threshold to allow for discrimination of inflammatory and non-inflammatory joint disease.

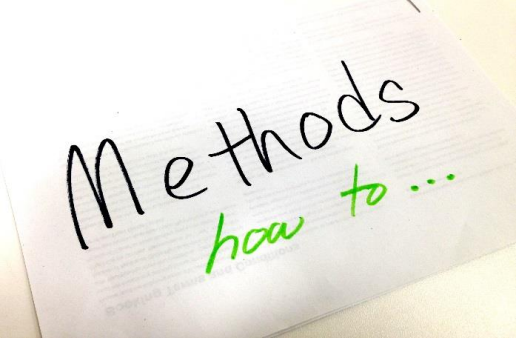
FIG. 1 Distribution of CDUS sum scores in relation to OA and IA.



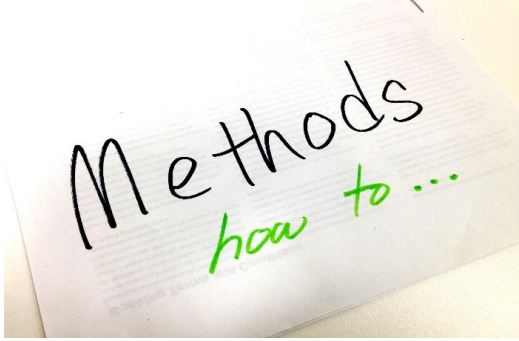


Purpose of the study

Evaluation of the effectiveness of the different treatment (HA – CS) with joints injections in patients with knee Osteoarthritis

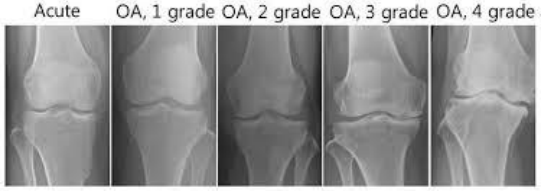


MATERIALS & METHODS



We evaluated a cohort of patients affected by

- OA of the knee whose diagnosis had been made by using the ACR criteria
- Grade 2-3 of the Kellgren-Lawrence's classification



All the patients have been monitored for 6 months

•The measurement of subjective pain using the 10 cm-visual analogue scale/VAS

•The measurement of pain, stiffness, and functionality by using the Western Ontario and McMaster Universities Arthritis Index-WOMAC

•US with an evaluation of both the synovial Gray Scale and the PWD signal (the OMERACT scale 0-3)

SAMPLE

155 pt

Group A: 52 HA>1500 Kda (3 US g.i. one week apart)

Group B: 56 HA 80-1200 Kda (3 US g.i. one week apart)

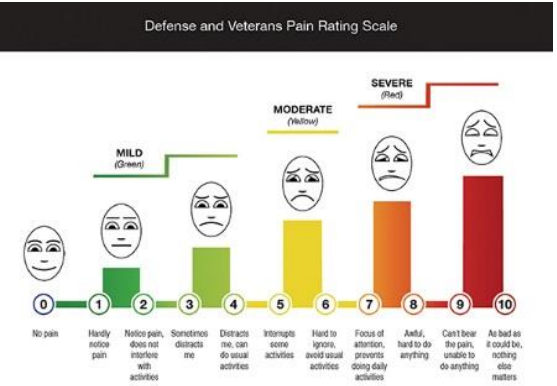
Group C: 47 Corticosteroids (3 US g.i. one week apart)

♂ 27.7% 64.6 years old (SD±7.3)

♀ 72.3% 69.3 years old (SD±4.1).

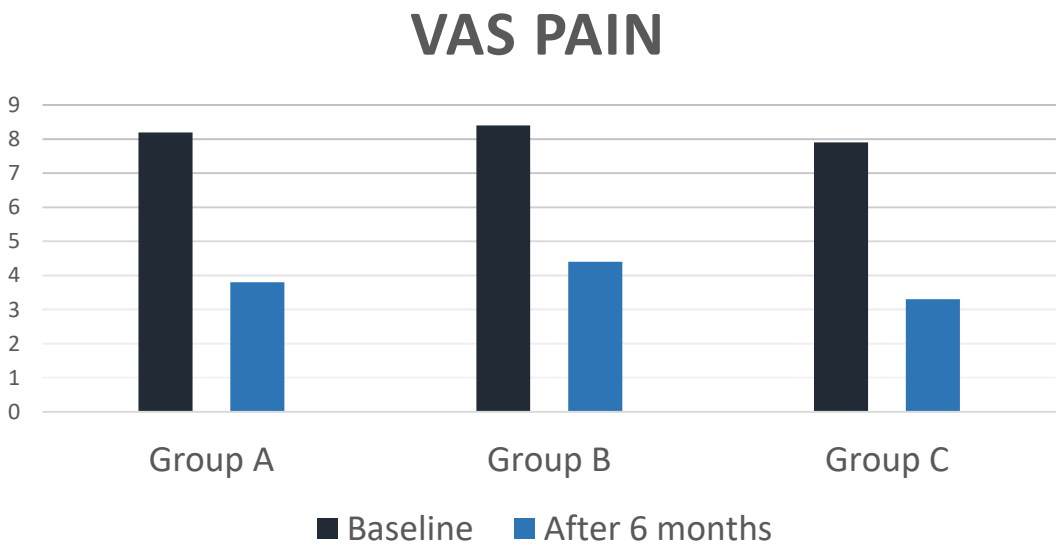

We performed 103 bilateral and 52 monolateral
774 joint injections in total

RESULTS



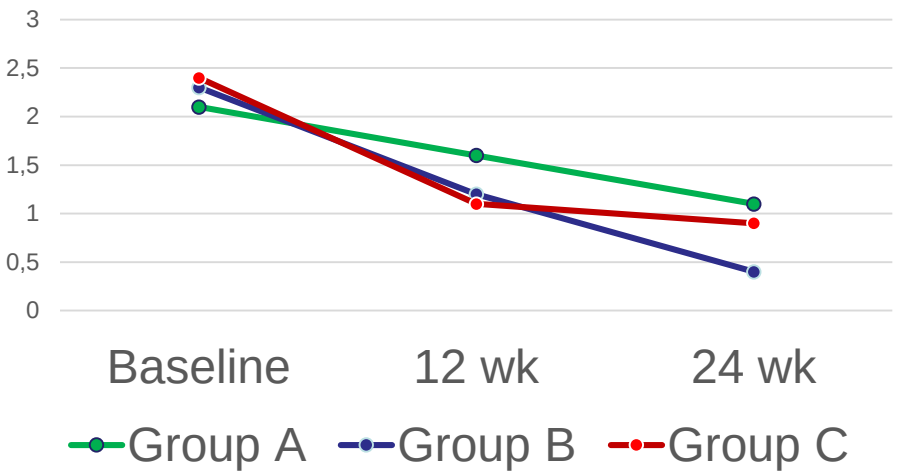
RESULTS

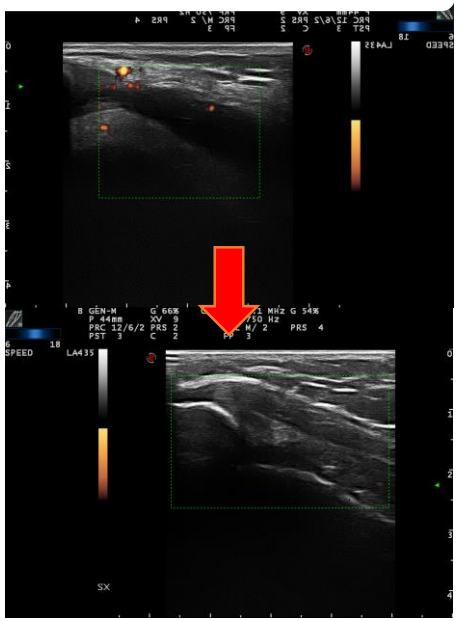
All the evaluated subjects showed a pain relief 6 months after the treatment (GrA:46.5% - GrB:52.8% - GrC:41.3% p=0.005).



WOMAC was statistically significantly better than its baseline in all the considered groups [57.0% (95% CI: 54.6 to 60.8) to 71.6 (95% CI: 68.3 to 75.1 - p=0.001], with no differences between the groups (K-W p-value 0,856). The WOMAC total score improvement was higher in patients with a Kellen-Lawrence's grade 2 (p-value= 0.026).

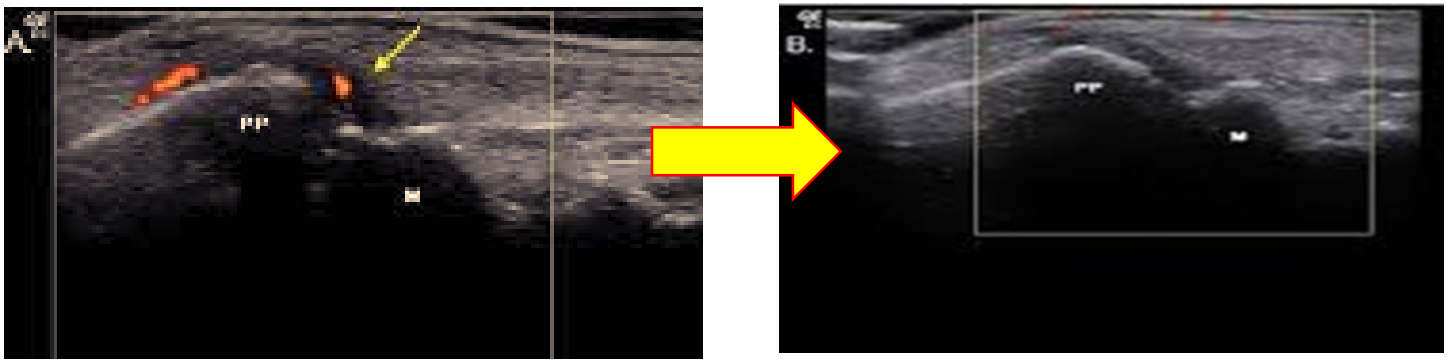
RESULTS





PWD signal got better in group B (p-value 0.001) and C (p-value 0.011) 3 months after the treatment. Furthermore, in group B the PWD signal proved to be statistically significantly decreased after 6 months as well (p= 0.035)

THE ROLE OF PWD



The exact mechanism through which intra-articular HA promotes pain relief is not clearly understood, although the upregulation of cartilage synthesis as well as the inhibition of inflammatory cytokines have been proposed.

Ingegnoli et al. Power Doppler sonography and clinical monitoring for hyaluronic acid treatment of rhizarthrosis: a pilot study. J.Hand Micros. 2011 Dec: 3(2):51-4

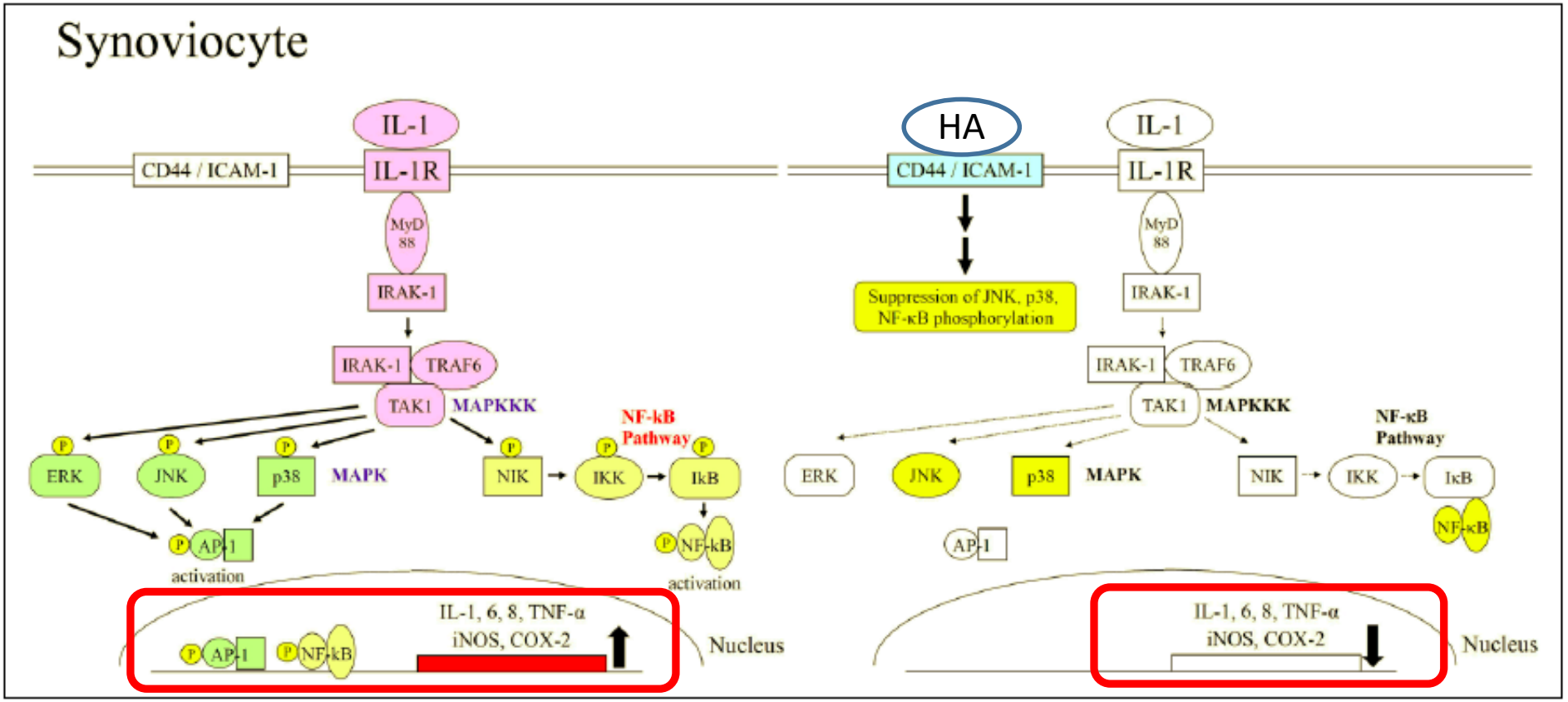


Figure 2. Upregulation of inflammatory gene expressions by IL-1 and the molecular mechanism of its downregulation by Supartz FX in synoviocytes. The binding of IL-1 to its receptor on cell surface activates MAP kinase and NF-κB signal transductions in synoviocytes. These signal transductions induce activation of AP-1 and NF-κB transcription factors, and inflammatory gene expressions are upregulated by these transcription factors. The binding of Supartz FX to CD44 or ICAM-1 suppresses phosphorylation of JNK, p38, and NF-κB. These molecular changes inactivate AP-1 and NF-κB, and inflammatory gene expressions are downregulated.

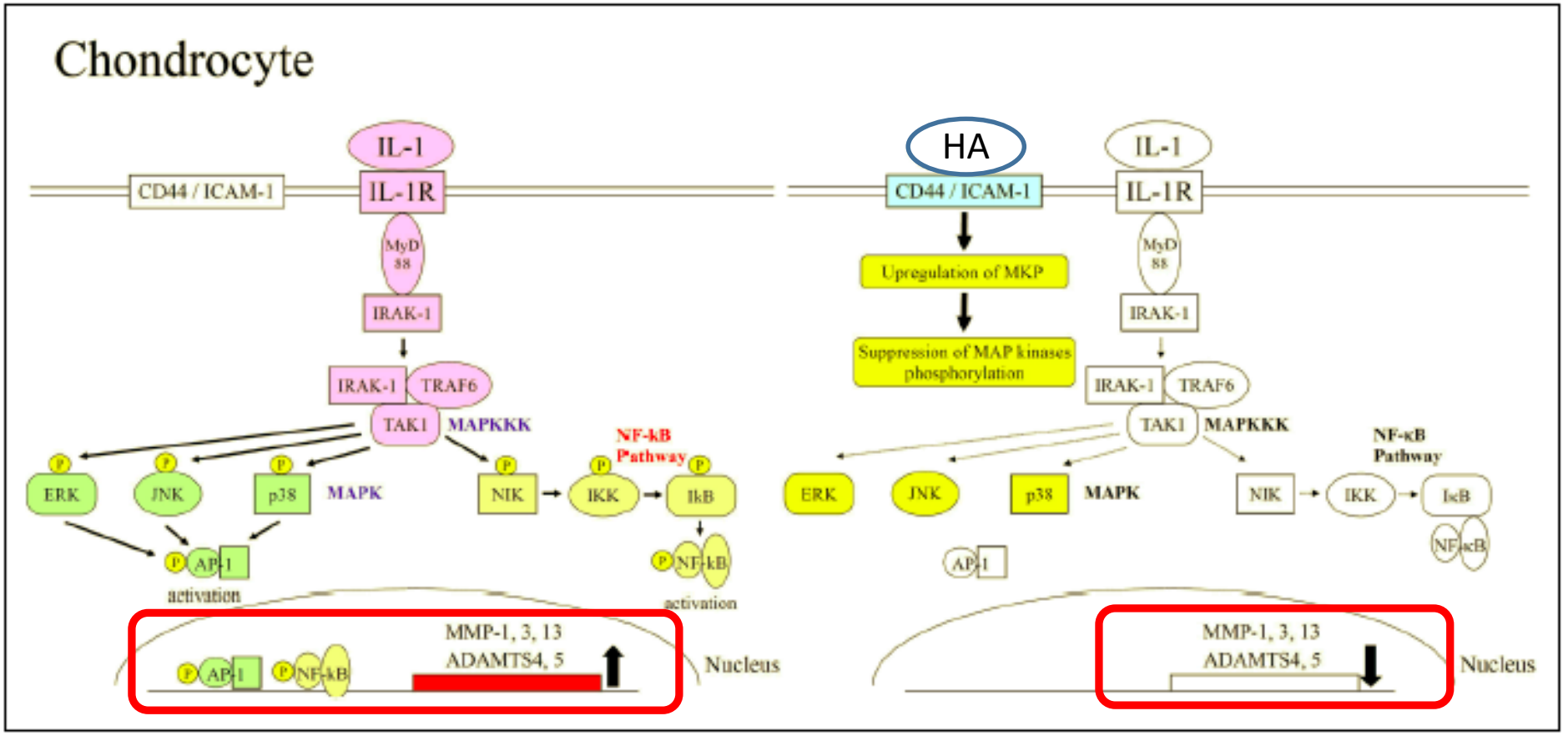


Figure 3. Upregulation of MMP and ADAMTS gene expressions by IL-1 and the molecular mechanism of its downregulation by Supartz FX in chondrocytes. As in synoviocytes, the binding of IL-1 to its receptor activates MAP kinase and NF-κB signal transductions in chondrocytes. These signal transductions induce activation of AP-1 and NF-κB transcription factors, and MMP and ADAMTS gene expressions are upregulated by these transcription factors. The binding of Supartz FX to CD44 or ICAM-1 suppresses phosphorylation of MAP kinases. These molecular changes inactivate AP-1, and MMP and ADAMTS gene expressions are downregulated.

CONCLUSIONI

- **La terapia intra-articolare costituisce un valido supporto al trattamento dei pazienti affetti da OA sintomatica in particolar modo di ginocchio ed anca**
- **La terapia infiltrativa con HA sembra comunque essere una procedura relativamente sicura e con scarsi effetti collaterali sistemici**
- **Permette la riduzione dell'assunzione complessiva di farmaci anti-infiammatori non steroidei**

CONCLUSIONI

- **Preparato steroideo di scelta nella terapia intra-artcolare è risultato essere il triamcinolone esacetonide**
- **La terapia steroidea sembra avere un efficacia più limitata nel tempo**
- **La terapia intra-articolare con concentrato piastrinico autologo sembra essere un' ulteriore alternativa**

CONCLUSIONI

- **Ottimizzazione della Tecnica Infiltrativa con metodica ecografica**
- **Efficacia del Medio Peso Molecolare nel trattamento dei pazienti con coinvolgimento sinoviale**
- **La riduzione delle MMP potrebbe in parte spiegare la particolare efficacia nei pazienti con coinvolgimento infiammatorio sinoviale**

ADAPTE SIR OSTEOARTROSI

P650

THE ITALIAN RHEUMATOLOGY SOCIETY ADAPTATION OF RECOMMENDATIONS ON KNEE, HIP AND HAND OSTEOARTRITIS: THE OA SIR-ADAPTE PROJECT

Correspondence to
dott.alaricoariani@libero.it

Alarico Ariani[1], M. Manara[2], N. Ughi[3], I. Prevete[4], S. Parisi[5], A. Bortoluzzi[6], G. Carrara[7], F. Rumi[7], A. Zanetti[7], A. Fioravanti[8], F. Iannone[9], F. Salaffi[10], C. A. Scirè[6],