APPROCCI INTERDISCIPLINARI IN REUMATOLOGIA

9ª edizione

RIABILITAZIONE E MALATTIE REUMATICHE

TORINO, 8-9 ottobre 2021

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

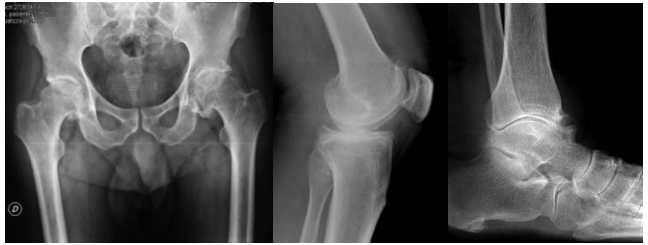
IL SUPPORTO DELLA TERAPIA INFILTRATIVA NEL TRATTAMENTO DELL'OSTEOARTROSI E DEI REUMATISMI INFIAMMATORI

Simone Parisi

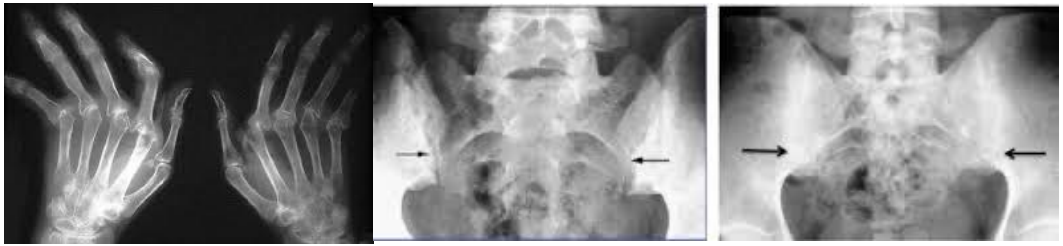
AOU Città della Salute e della Scienza di Torino
SC Reumatologia

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

ABBVIE, AMGEN, BIOGEN, BMS, CELGENE, CHIESI, FRESENIUS, JANSSEN, MSD, NOVARTIS, PFIZER, LILLY, SANOFI, UCB



OSTEOARTROSI



MALATTIE REUMATICHE MSK

TERAPIA

CONTROLLO DEL SINTOMO

SINTOMATICI

FANS

Analgesici

STEROIDI

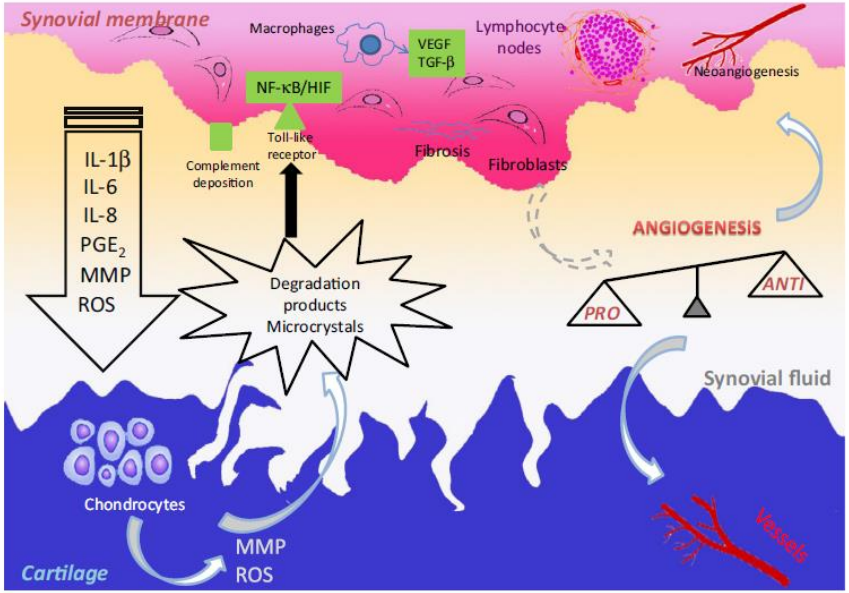
CONTROLLO DEL DANNO STRUTTURALE

cs/ts/bDMARD (disease modifying anti rheumatic drug)

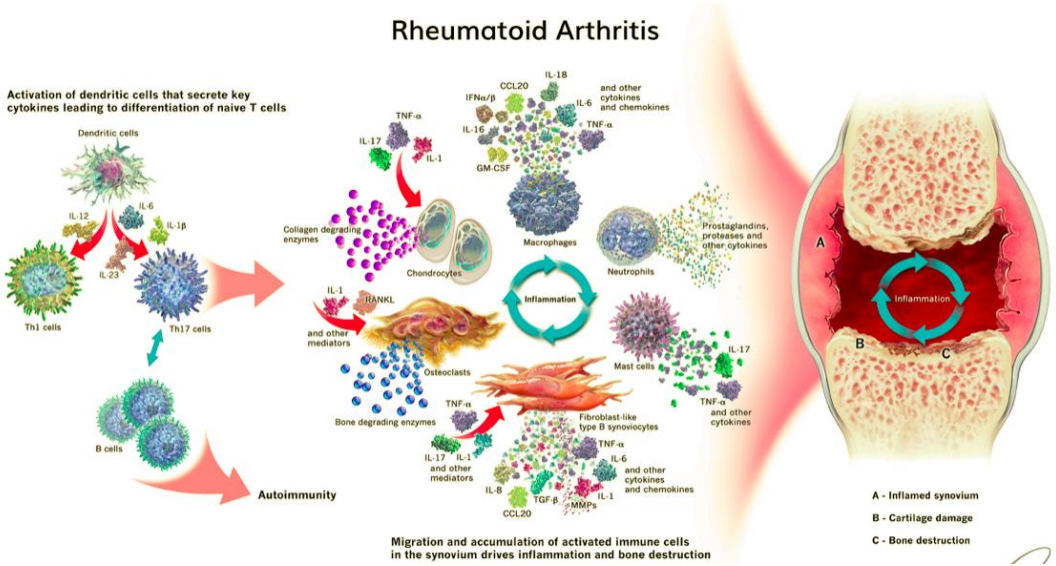
SYSADOA (slow-acting drug for OA)

DMOAD (disease modifying drug for OA)

IMMUNOPATOGENESI



From Henrotin Y



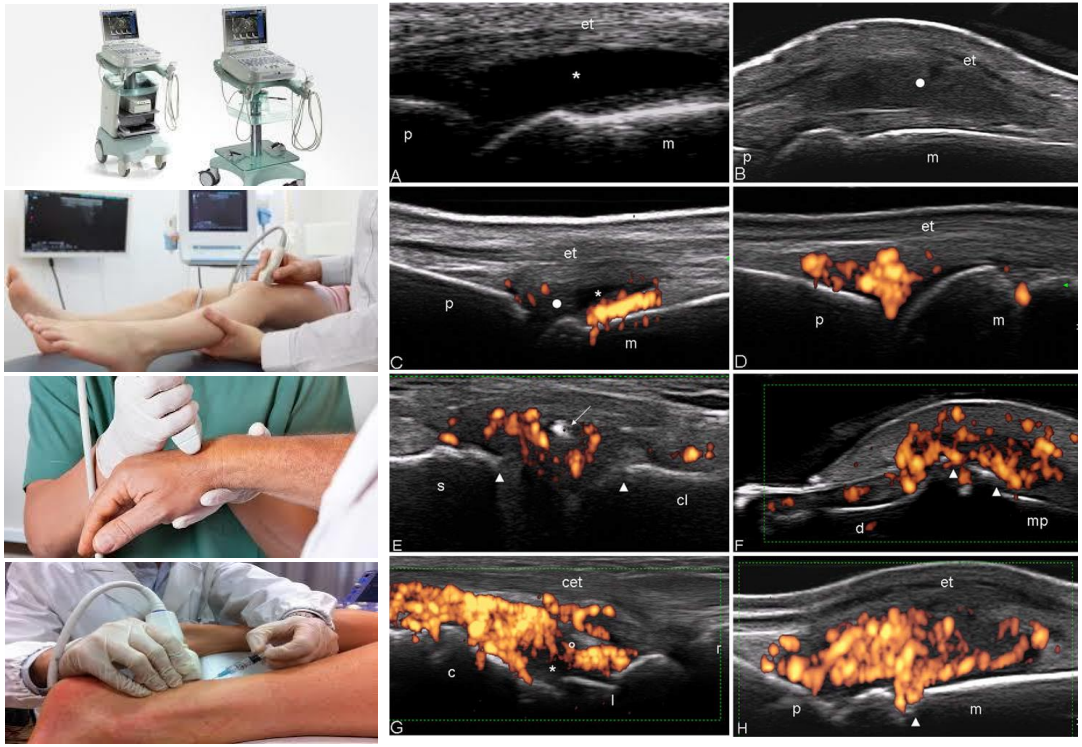
From Geras A.

OBIETTIVI DEL TRATTAMENTO

- RIDUZIONE DEL DOLORE
- MANTENIMENTO DEL FUNZIONALITA' ARTICOLARE
- CONTENIMENTO DELLA DISABILITA'
- RALLENTAMENTO/BLOCCO DELLA PROGRESSIONE DI MALATTIA

- PREVENZIONE
- TERAPIA MEDICA
- TERAPIA FISICA
- TERAPIA CHIRURGICA

IL RUOLO DELL'ECOGRAFIA



Osteoarthritis and Cartilage 22 (2014) 1627–1633

Osteoarthritis and Cartilage

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Synovial pathology detected on ultrasound correlates with the severity of radiographic knee osteoarthritis more than with symptoms

M. Hall †‡*, S. Doherty †, P. Courtney §, K. Latief §, W. Zhang †, M. Doherty †

† Academic Rheumatology, University of Nottingham, UK
‡ School of Health Sciences, University of Nottingham, UK
§ Nottingham University Hospitals NHS Trust, UK

- US features, particularly synovial hypertrophy, may well have a role to play in the development of painful OA.
- Synovial abnormalities are more common in those with painful knee OA compared to those with asymptomatic OA or normal knees.
- The presence of increased PD signal within the synovium is suppurported to represent more active inflammation.
- The association between individual US features and pain is not coclusive

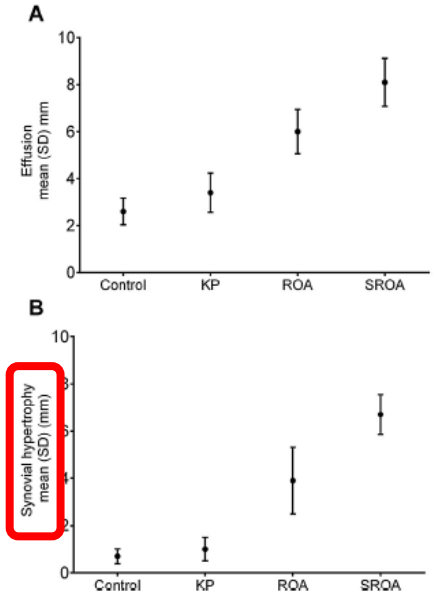
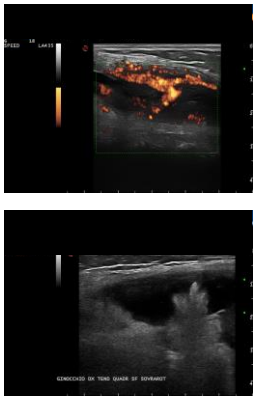


Fig. 2. US measures of (A) effusion and (B) synovial hypertrophy for each group.



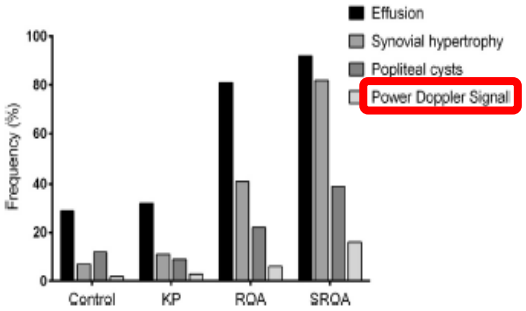


Fig. 1. Bar chart showing frequency (%) of US features within each comparison group.

Clinical Interventions in Aging

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REVIEW

Clinical utility of ultrasound guidance for intra-articular knee injections: a review

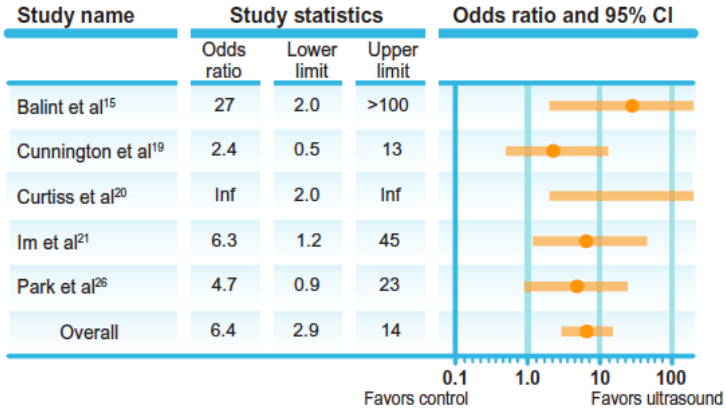
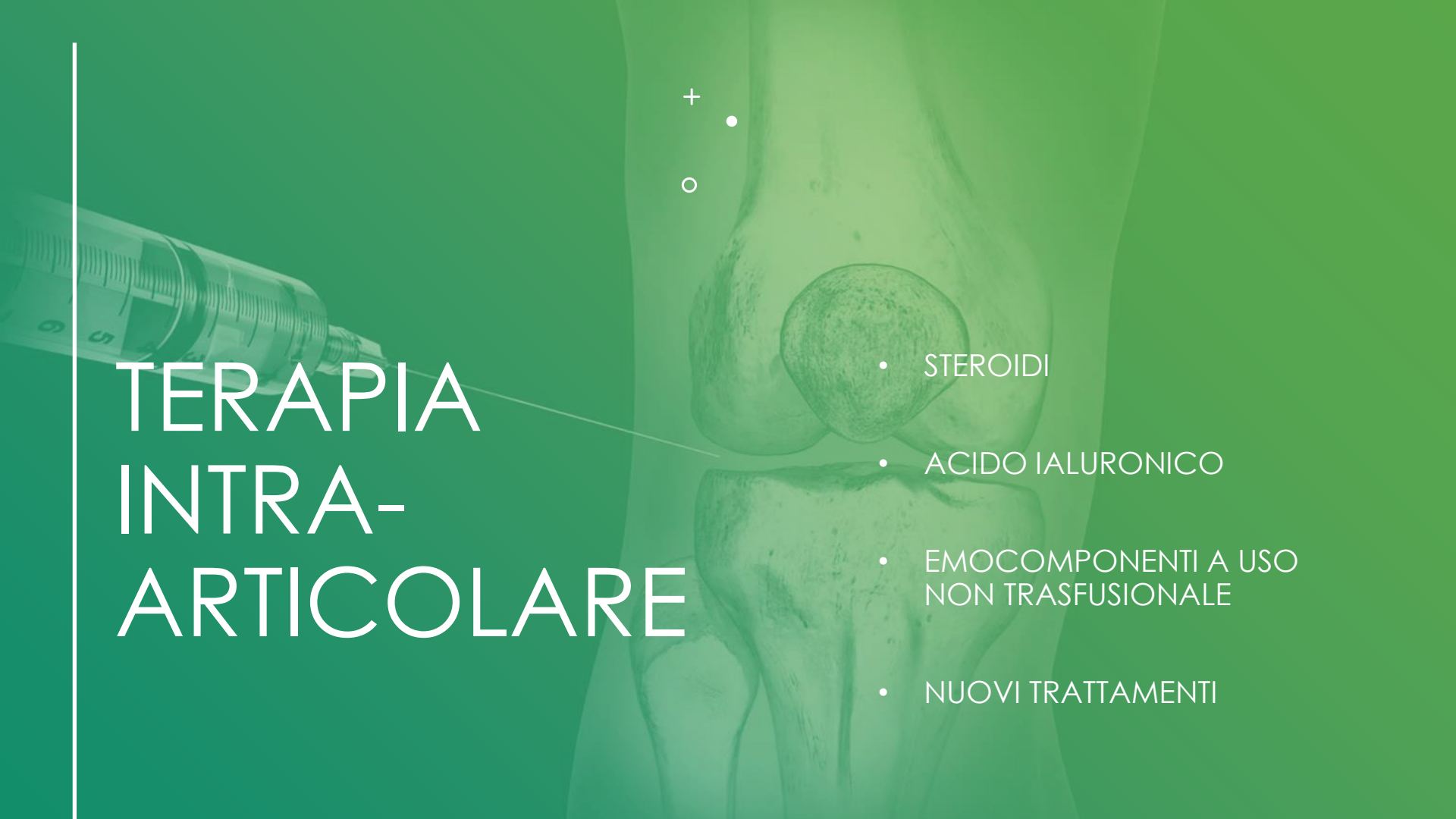


Figure 1 Accuracy of ultrasound guidance for intra-articular knee injections: forest plot of controlled studies.

Compared with anatomical guidance, ultrasound guidance reduced injection pain by 81% (P = 0.001) and increased therapeutic duration by 32% (P = 0.01)

TERAPIA INTRA-ARTICOLARE



- STEROIDI
- ACIDO IALURONICO
- EMOCOMPONENTI A USO NON TRASFUSIONALE
- NUOVI TRATTAMENTI

Reumatismo, 2019; 71 (S1): 5-22

RASSEGNA

Raccomandazioni della Società Italiana di Reumatologia sulla diagnosi e trattamento dell'artrosi di ginocchio, anca e mano

The Italian Society for Rheumatology clinical practice guidelines for the diagnosis and management of knee, hip and hand osteoarthritis

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

[1]Centro Studi, Società Italiana di Reumatologia, Milano; [2]Dipartimento di Medicina, Unità di Medicina Interna e Reumatologia, Azienda Ospedaliero-Universitaria di Parma; [3]Reumatologia Clinica, Centro Specialistico Ortopedico-Traumatologico Gaetano Pini CTO, ASST Gaetano Pini, Milano; [4]Unità di Reumatologia, Azienda Ospedaliero Universitaria Senese, Siena; [5]Dipartimento di Emergenza e Trapianti d'Organo, Unità di Reumatologia, Università di Bari; [6]Clinica Reumatologica, Ospedale Carlo Urbani, Università Politecnica delle Marche, Jesi (AN); [7]Unità di Reumatologia, Azienda Ospedaliera San Camillo-Forlanini, Roma; [8]Dipartimento di Scienze Mediche, Sezione di Reumatologia, Università di Ferrara, Azienda Ospedaliero-Universitaria Sant'Anna di Cona, Ferrara; [9]Unità di Reumatologia, Azienda Ospedaliera Città della Salute e della Scienza di Torino

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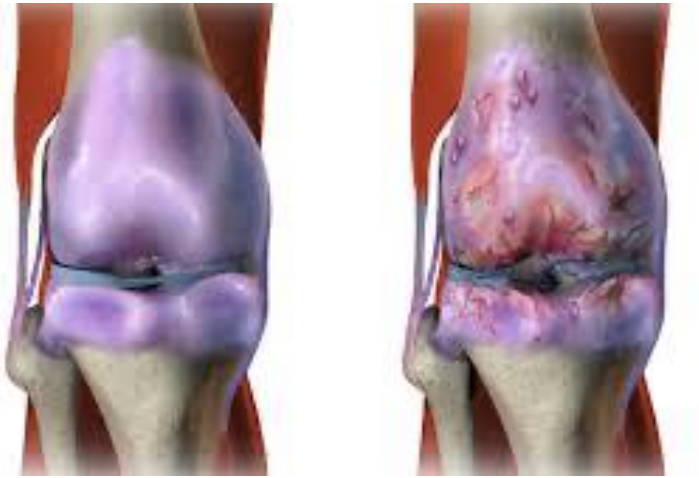
N.	Raccomandazione	Livello
8	Il paracetamolo (fino a 3 g/die) è una iniziale ed efficace terapia orale per soggetti con dolore lieve-medio. Negli anziani dovrebbe essere preferito anche per il relativo grado di sicurezza rispetto a quello dei FANS. Si raccomanda l'impiego di oppioidi deboli in caso di dolore marcato, inefficacia, perdita della risposta, intolleranza o controindicazione all'uso dei FANS. In casi eccezionali si può ricorrere ad oppioidi più forti. La duloxetina può essere d'aiuto nell'OA di ginocchio (e verosimilmente di anca) associata a dolore cronico.	1-4
9	I FANS orali sono raccomandati alla minima dose efficace e per il minimo tempo necessario in tutti quei pazienti che rispondono in modo non adeguato al paracetamolo. FANS (come l'ibuprofene, naprossene e diclofenac) ed inibitori della COX2 (compreso sia etoricoxib che celecoxib) sono indicati nel dolore di grado medio. Dosi maggiori sono da impiegare in caso di dolore più rilevante. Nei pazienti con rischio gastro-intestinale incrementato dovrebbero essere impiegati i FANS non selettivi in associazione ad un inibitore di pompa, oppure un inibitore selettivo della COX2. In pazienti con elevato rischio cardiovascolare dovrebbe essere usato il naprossene; gli inibitori della COX2 sono controindicati mentre gli altri FANS dovrebbero essere usati con cautela.	1
10	I trattamenti farmacologici topici sono da preferirsi a quelli sistemici, in particolare nel caso di dolore lieve-moderato e quando sono colpite solo poche articolazioni. I FANS topici e i gel a base di capsaicina sono trattamenti sicuri ed efficaci. Pazienti con più di 75 anni dovrebbero preferire formulazioni topiche piuttosto che FANS per via orale, anche se l'effetto del trattamento topico tende a scemare dopo il primo anno di utilizzo.	1-2
11	In generale la precisione delle infiltrazioni intra-articolari dipende dall'articolazione e dall'abilità di chi la effettua. La guida ecografica può migliorare la precisione ed è particolarmente raccomandata per le articolazioni di difficile accesso per posizione, stadio anatomico od obesità. Acido ialuronico: le infiltrazioni di acido ialuronico di diverso peso molecolare possono portare a benefici sintomatici con minima tossicità e possono ridurre l'uso dei FANS. Steroidi: infiltrazioni intra-articolari con corticosteroidi possono essere di beneficio perché portano ad un rapido controllo dei sintomi nei soggetti che sono affetti da riacutizzazioni dolorose e che non rispondono o hanno controindicazioni all'uso di analgesici o di FANS. Cellule staminali mesenchimali e gel piastrinico: non è chiaro se le infiltrazioni intra-articolari di cellule staminali mesenchimali o gel piastrinico possano contribuire ad alleviare il dolore associato all'OA del ginocchio.	1-5
12	Nei pazienti con OA del ginocchio sintomatica la glucosamina solfato e il condroitin solfato potrebbero avere effetti benefici sui sintomi; restano da definire i loro effetti strutturali, i pazienti idonei al trattamento e la convenienza farmaco-economica della terapia.	1-2

Arthritis Care & Research
Vol. 72, No. 2, February 2020, pp 149–162
DOI 10.1002/acr.24131

American College of Rheumatology
Empowering Rheumatology Professionals

2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee

Sharon L. Kolasinski,[1] Tuhina Neogi,[2] Marc C. Hochberg,[3] Carol Oatis,[4] Gordon Guyatt,[5] Joel Block,[6] Leigh Callahan,[7] Cindy Copenhaver,[8] Carole Dodge,[9] David Felson,[2] Kathleen Gellar,[10] William F. Harvey,[11] Gillian Hawker,[12] Edward Herzig,[13] C. Kent Kwoh,[14] Amanda E. Nelson,[7] Jonathan Samuels,[15] Carla Scanz Daniel White,[16] Barton Wise,[17] Roy D. Altman,[18] Dana DiRenzo,[19] Joann Fontanarosa,[20] Gina Giradi,[20] Mariko Ishimori,[21] Devyani Misra,[2] Amit Aakash Shah,[22] Anna K. Shmagel,[23] Louise M. Thoma,[7] Marat Turgunbaev,[22] Amy S. Turner,[22] and James Reston[20]



OA is challenging to manage

- No cure or remission
- No strategy to reduce progression
- No proven way to prevent joint replacement
- Structural damage is irreversible and progressive
- Available pharmacologic treatments are associated with significant adverse events

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- **Recommendations Strong**
- Exercise (Physical activity is key for ALL MSK pain
- Weight Loss, Tai Chi, Canes
- Thumb and knee bracing
- Oral NSAIDs (considering risks)
- Knee: topical NSAIDs
- **Knee/Hip: IA corticosteroids**

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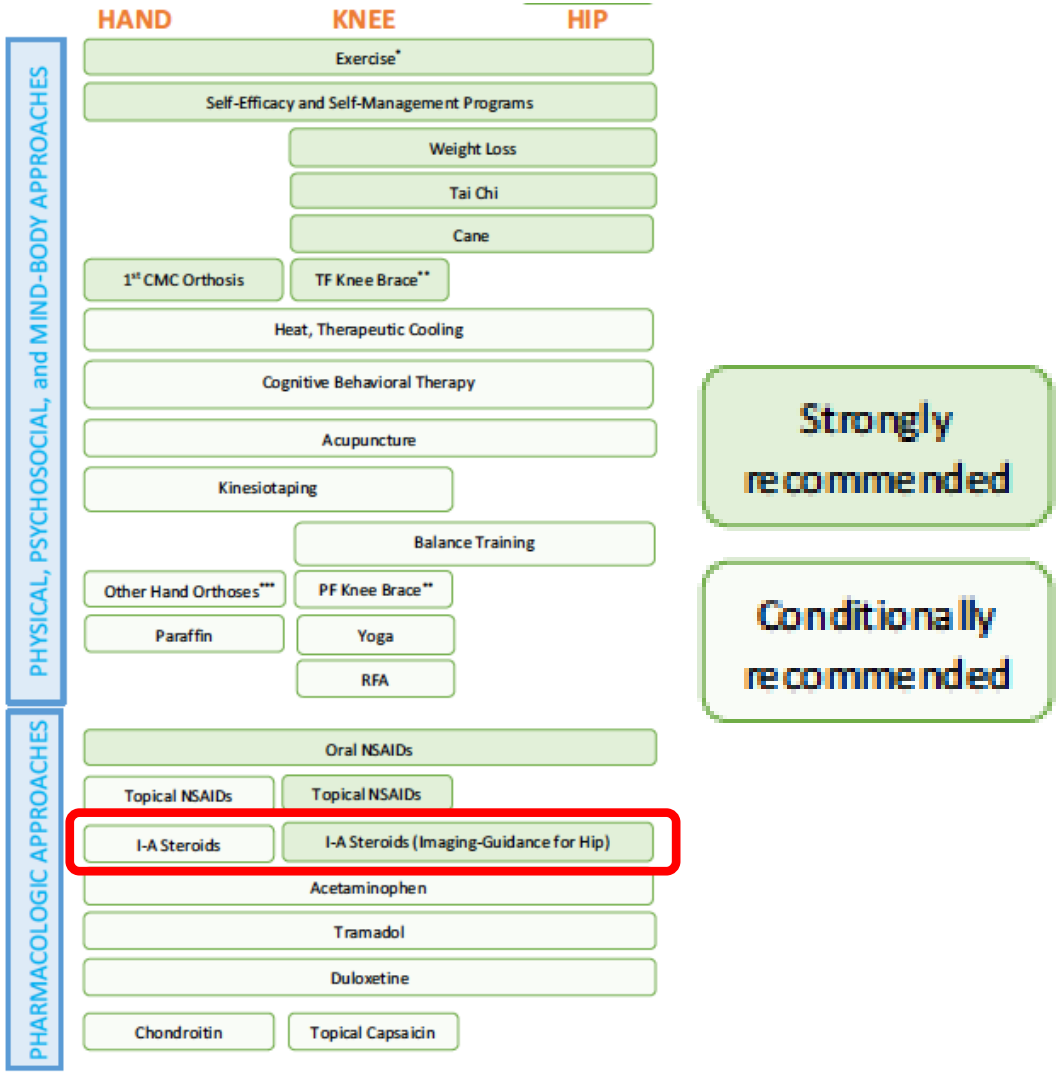
ACR 2020
Conditionally NR

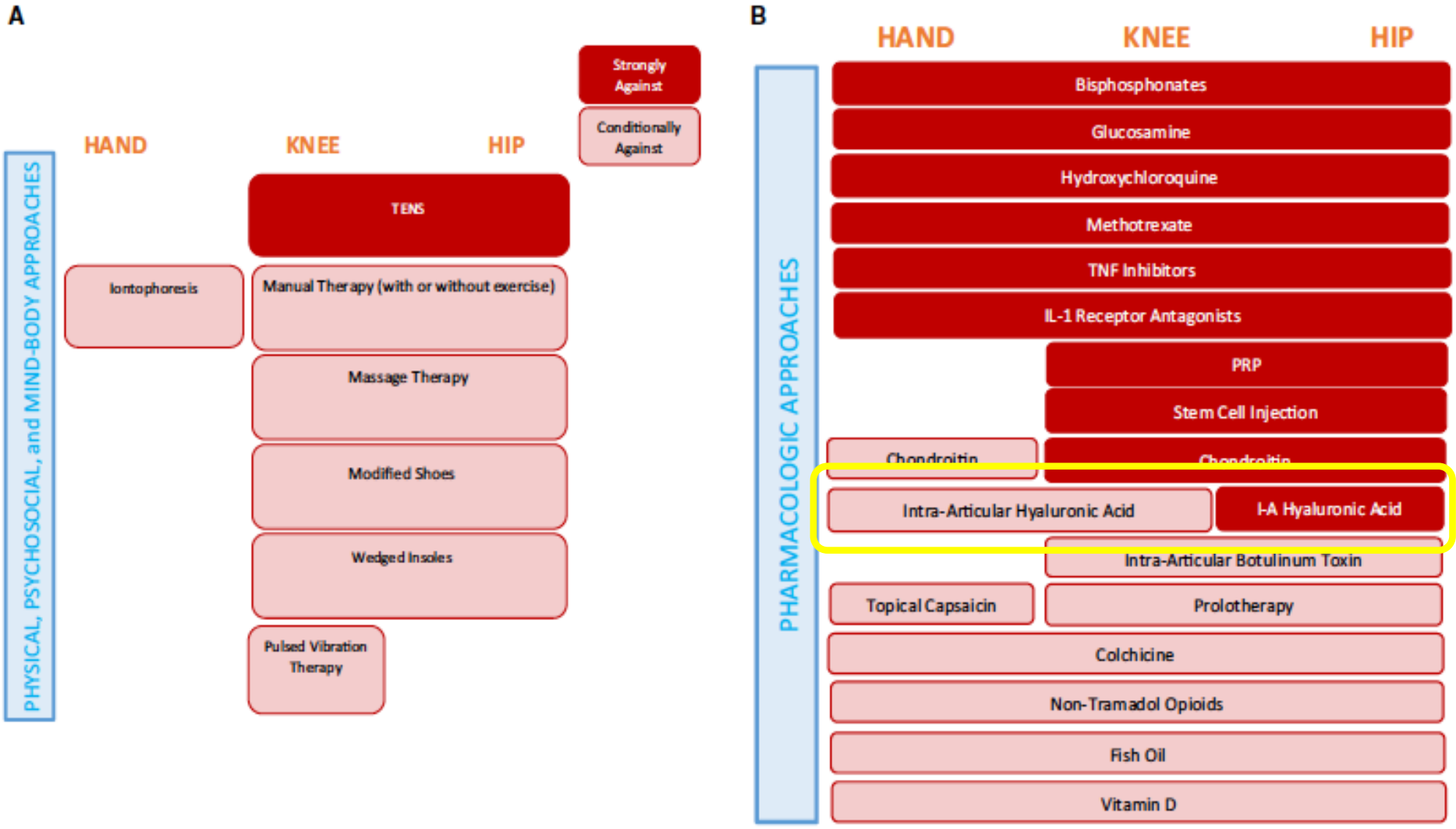
CONTROVERSIAL TREATMENTS

IAHA

PRP

MSC


HAND
KNEE
HIP
PHYSICAL, PSYCHOSOCIAL, and MIND-BODY APPROACHES
Exercise*
Self-Efficacy and Self-Management Programs
Weight Loss
Tai Chi
Cane
1st CMC Orthosis
TF Knee Brace**
Heat, Therapeutic Cooling
Cognitive Behavioral Therapy
Acupuncture
Kinesiotaping
Balance Training
Other Hand Orthoses***
PF Knee Brace**
Paraffin
Yoga
RFA
PHARMACOLOGIC APPROACHES
Oral NSAIDs
Topical NSAIDs
Topical NSAIDs
I-A Steroids
I-A Steroids (Imaging-Guidance for Hip)
Acetaminophen
Tramadol
Duloxetine
Chondroitin
Topical Capsaicin
Strongly recommended
Conditionally recommended


A
Strongly Against
Conditionally Against
HAND
KNEE
HIP
PHYSICAL, PSYCHOSOCIAL, and MIND-BODY APPROACHES
TENS
Iontophoresis
Manual Therapy (with or without exercise)
Massage Therapy
Modified Shoes
Wedged Insoles
Pulsed Vibration Therapy
B
HAND
KNEE
HIP
PHARMACOLOGIC APPROACHES
Bisphosphonates
Glucosamine
Hydroxychloroquine
Methotrexate
TNF Inhibitors
IL-1 Receptor Antagonists
PRP
Stem Cell Injection
Chondroitin
Chondroitin
Intra-Articular Hyaluronic Acid
I-A Hyaluronic Acid
Intra-Articular Botulinum Toxin
Topical Capsaicin
Prolotherapy
Colchicine
Non-Tramadol Opioids
Fish Oil
Vitamin D

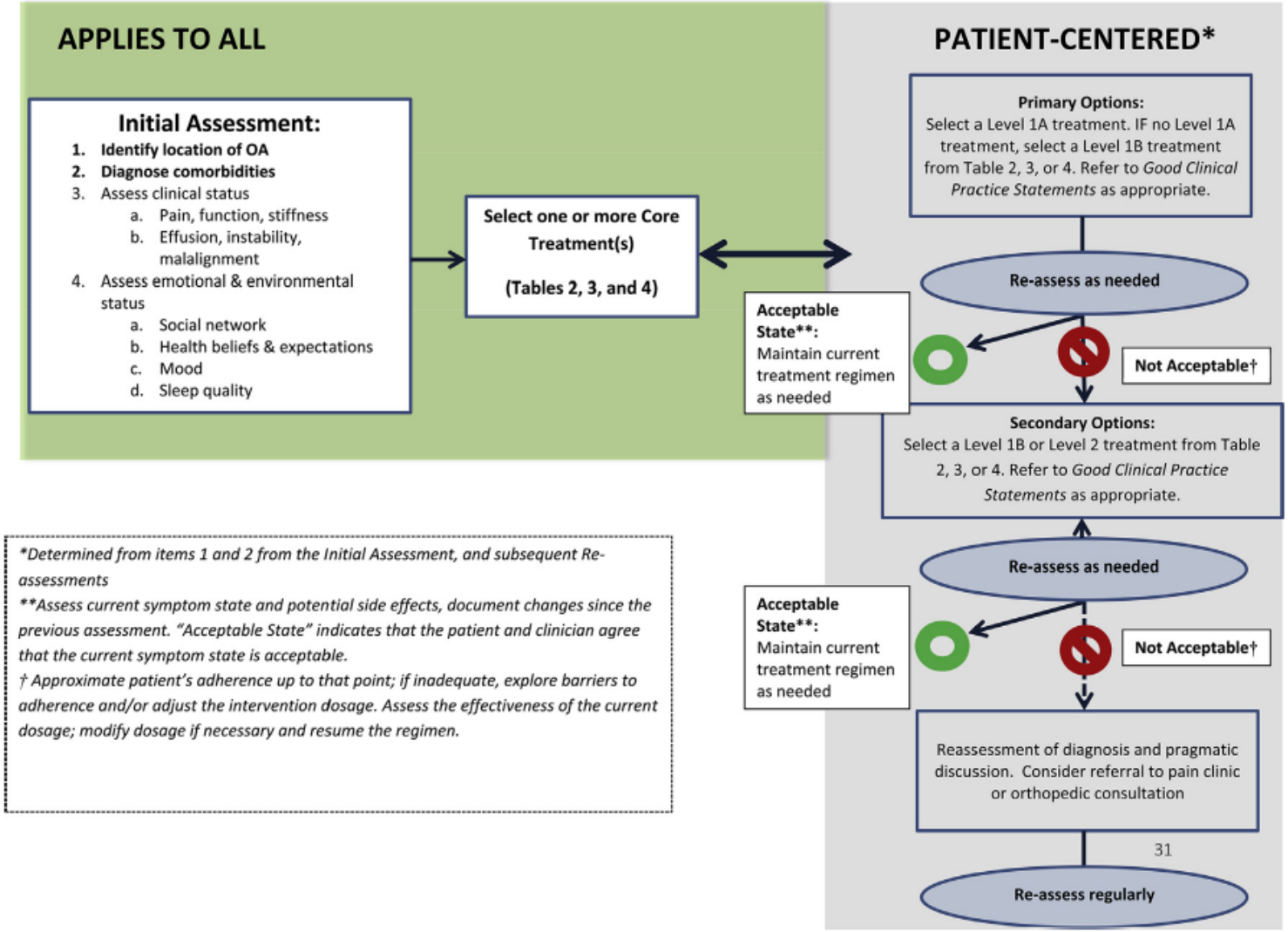
Osteoarthritis and Cartilage 27 (2019) 1578–1589

Osteoarthritis and Cartilage

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis

R.R. Bannuru † *, M.C. Osani †, E.E. Vaysbrot †, N.K. Arden ‡ §, K. Bennell ‖, S.M.A. Bierma-Zeinstra ¶ #, V.B. Kraus ††, L.S. Lohmander ‡‡, J.H. Abbott §§, M. Bhandari ‖‖, F.J. Blanco ¶¶ ##, R. Espinosa ††† ‡‡‡, I.K. Haugen §§§, J. Lin ‖‖‖, L.A. Mandl ¶¶¶, E. Moilanen ###, N. Nakamura ††††, L. Snyder-Mackler ‡‡‡‡, T. Trojian §§§§, M. Underwood ‖‖‖‖ ¶¶¶¶, T.E. McAlindon †



Determined from items 1 and 2 from the Initial Assessment, and subsequent Re-assessments

***Assess current symptom state and potential side effects, document changes since the previous assessment. "Acceptable State" indicates that the patient and clinician agree that the current symptom state is acceptable.*

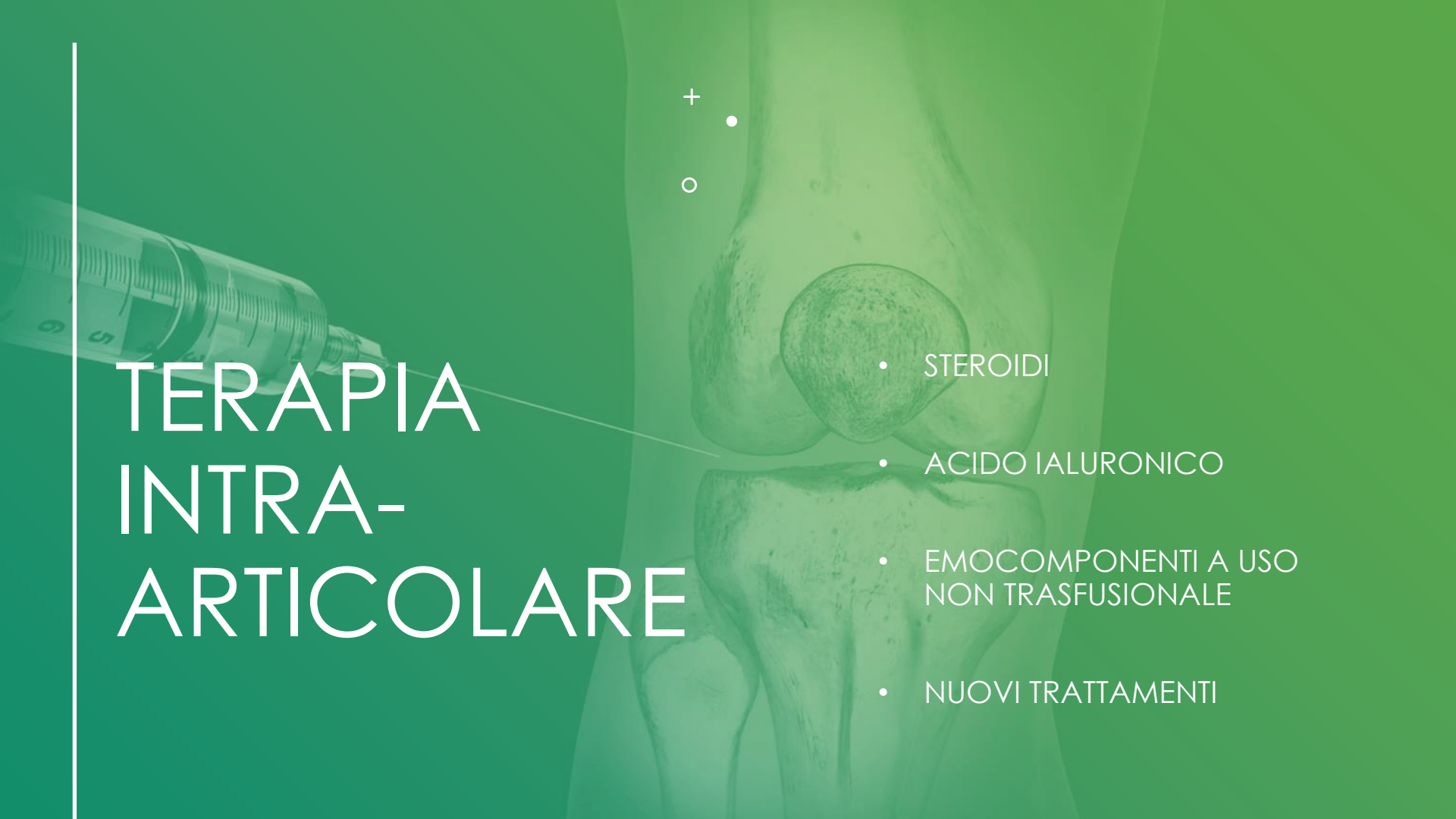
† Approximate patient's adherence up to that point; if inadequate, explore barriers to adherence and/or adjust the intervention dosage. Assess the effectiveness of the current dosage; modify dosage if necessary and resume the regimen.

Table II
Recommended treatments, by level, for knee osteoarthritis

Recommendation level	Strength	Treatment type	No comorbidities	Gastrointestinal	Cardiovascular	Frailty	Widespread pain/depression
CORE	Strong	Arthritis Education; Structured Land-Based Exercise Programs (Type 1- strengthening and/or cardio and/or balance training/neuromuscular exercise OR Type 2- Mind-body Exercise including Tai Chi or Yoga) with or without Dietary Weight Management					
Level 1A **High Consensus** *≥75% "in favor"*	Strong	Pharmacologic Non-Pharmacologic	Topical NSAIDs *refer to Level 1B*	Topical NSAIDs *refer to Level 1B*		Topical NSAIDs *refer to Level 1B*	*refer to Level 1B* *refer to Level 1B*
Level 1B **High Consensus** *≥75% "in favor" & >50% "conditional" Recommendation*	Conditional	Pharmacologic	• Non-selective NSAIDs • Non-selective NSAID + PPI • COX-2 Inhibitors IACS	COX-2 Inhibitors IACS, IAHA	IACS, IAHA	IACS, IAHA	• Non-selective NSAIDs • Non-selective NSAID + PPI • COX-2 Inhibitors
		Non-Pharmacologic	Aquatic Exercise, Gait Aids, Self-Management Programs	Aquatic Exercise, Gait Aids, Self-Management Programs		Aquatic Exercise, Gait Aids, Self-Management Programs	Aquatic Exercise, Cognitive Behavioral Therapy (with or without Exercise), Self-Management Programs, Gait Aids
Level 2 **Low Consensus** *60%-74% "in favor"*	Conditional	Pharmacologic Non-Pharmacologic	IAHA Cognitive Behavioral Therapy with Exercise	Non-selective NSAID + PPI Cognitive Behavioral Therapy with Exercise	*see below*	*see below* Cognitive Behavioral Therapy with Exercise	Duloxetine, IACS, IAHA, Topical NSAIDs *none recommended*
Good Clinical Practice Statements	Conditional	Various	*Intra-articular (IA) treatment*	*IA treatment, NSAID risk mitigation*		*IA treatment, NSAID risk mitigation*	*Pain management program, IA treatment*

IA treatment: Intra-articular corticosteroids (IACS) are conditionally recommended for acute (1–2 weeks) and short-term (4–6 weeks) pain relief; Intra-articular Hyaluronic Acid (IAHA) is conditionally recommended for longer term treatment effect, as it was associated with symptom improvement beyond 12 weeks and demonstrated a favorable safety profile.
NSAID risk mitigation: In situations where the patient and physician choose to proceed with an oral NSAID treatment regimen despite a lack of recommendation, we suggest using the lowest possible dose of oral NSAID for shortest treatment duration along with gastric protection with a PPI[23].
Pain management program: Based on clinical assessment, it may be appropriate to refer individuals of this phenotype to a multidisciplinary chronic/widespread pain management program.

TERAPIA INTRA-ARTICOLARE



- STEROIDI
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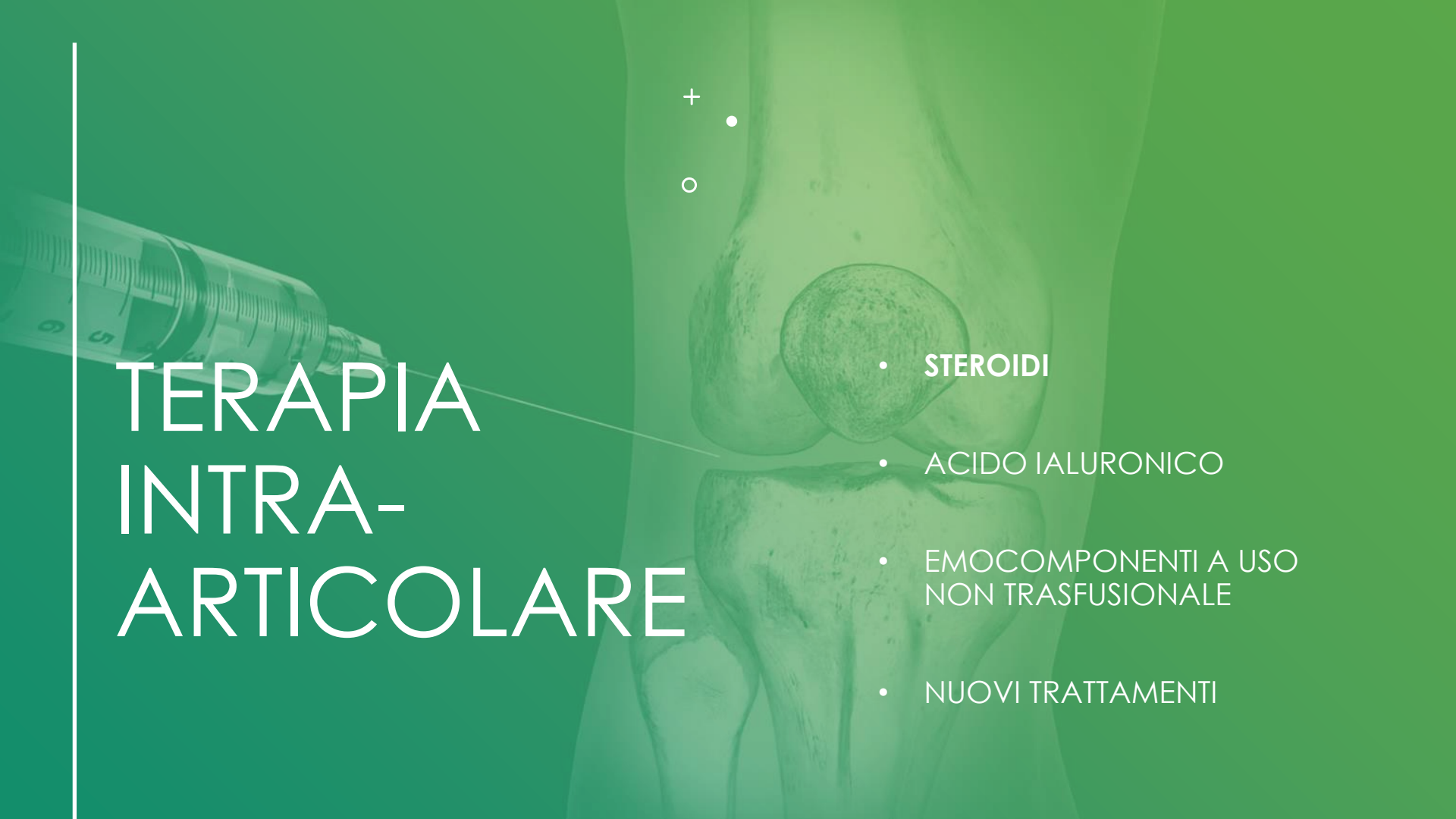
TERAPIA INTRA-ARTICOLARE



- **STEROIDI**
- ACIDO IALURONICO
- EMOCOMPONENTI A USO NON TRASFUSIONALE
- NUOVI TRATTAMENTI

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

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]
Frias 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)

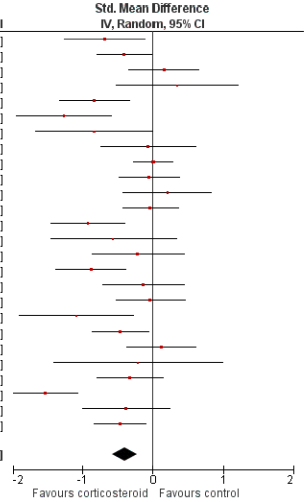
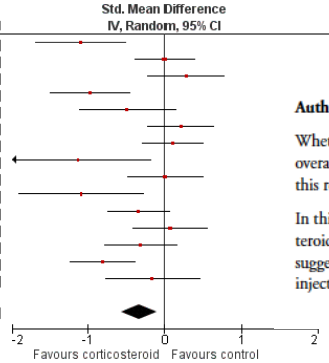


Figure 6. Forest plot of comparison: 2 Function, outcome: 2.1 Function - Main.

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: Tau² = 0.15; Chi² = 45.88, df = 14 (P < 0.0001); I² = 69%
Test for overall effect: Z = 2.70 (P = 0.007)



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.

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

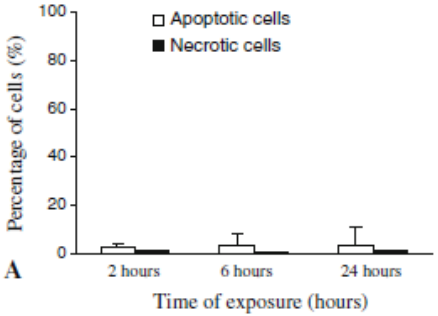
Boglárka Farkas MD, Krisztián Kvell MD, PhD, Tamás Czömpöly MD, PhD, Tamás Illés MD, PhD, Tamás Bárdos MD, PhD

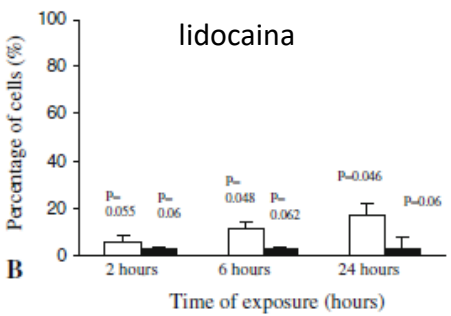
Methods Cell viability and apoptosis/necrosis assessment of human articular chondrocytes were performed in vitro (chondrocyte cell cultures) and ex vivo (osteochondral specimens) using flow cytometry and TUNEL analysis, respectively.

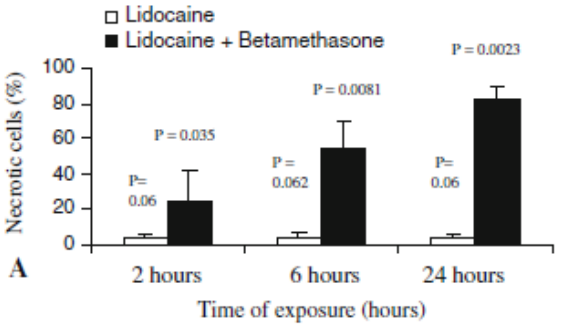
Table 1. Solutions and combinations used in the experiments*

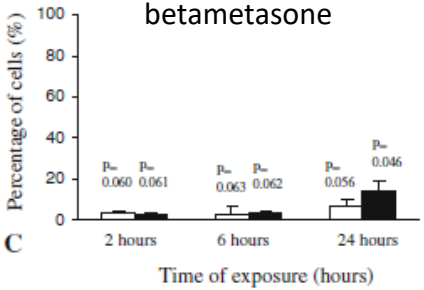
Agent	Concentration	Group number								
		I	II	III	IV	V	VI	VII	VIII	IX
Betamethasone	7 mg/mL	X					X	X	X	
Prednisolone	25 mg/mL		X							X
Lidocaine	10 mg/mL			X			X			X
Bupivacaine	5 mg/mL				X			X		
Ropivacaine	7.5 mg/mL					X			X	

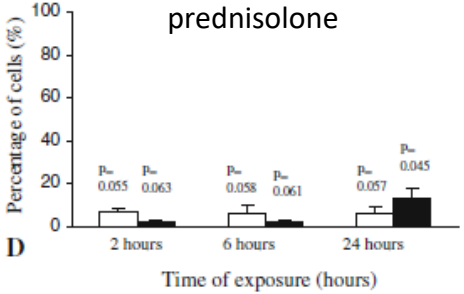
* Different steroids and local anesthetics were used alone or in combinations.

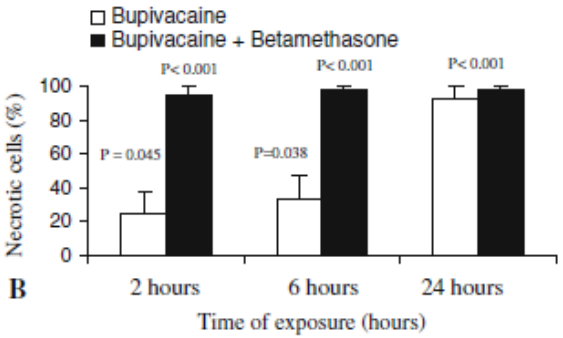

Apoptotic cells
Necrotic cells
Percentage of cells (%)
2 hours
6 hours
24 hours
Time of exposure (hours)
A

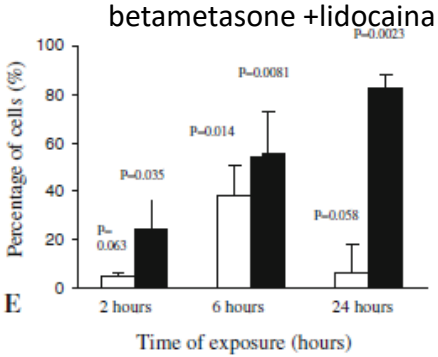

lidocaina
Percentage of cells (%)
P= 0.055
P= 0.06
P= 0.048
P= 0.062
P=0.046
P=0.06
2 hours
6 hours
24 hours
Time of exposure (hours)
B

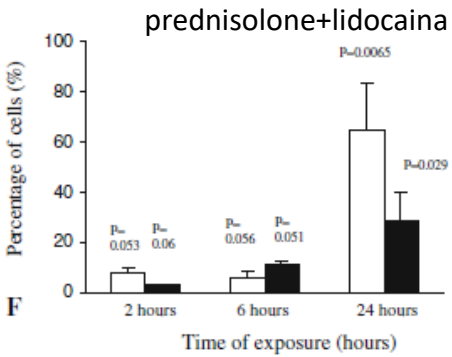

Lidocaine
Lidocaine + Betamethasone
Necrotic cells (%)
P= 0.06
P = 0.035
P = 0.062
P = 0.0081
P= 0.06
P = 0.0023
2 hours
6 hours
24 hours
Time of exposure (hours)
A


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


Bupivacaine
Bupivacaine + Betamethasone
Necrotic cells (%)
P = 0.045
P< 0.001
P=0.038
P< 0.001
P< 0.001
P< 0.001
2 hours
6 hours
24 hours
Time of exposure (hours)
B


betametasone +lidocaina
Percentage of cells (%)
P= 0.063
P=0.035
P=0.014
P=0.0081
P=0.058
P=0.0023
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

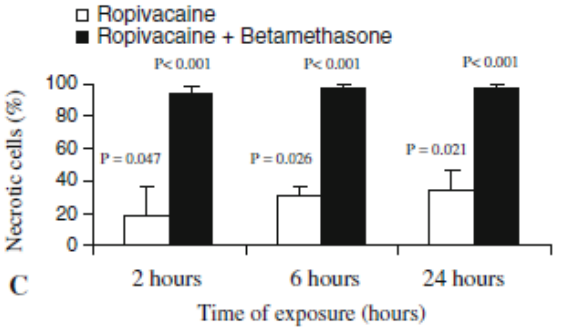

Ropivacaine
Ropivacaine + Betamethasone
Necrotic cells (%)
P = 0.047
P< 0.001
P = 0.026
P< 0.001
P = 0.021
P< 0.001
2 hours
6 hours
24 hours
Time of exposure (hours)
C

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%

Reumatismo, 2019; 71 (S1): 5-21 REVIEW

The Italian Society for Rheumatology clinical practice guidelines for the diagnosis and management of knee, hip and hand osteoarthritis

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

[1]Epidemiology Research Unit, Italian Society for Rheumatology (SIR), Milan, Italy; [2]Department of Medicine, Internal Medicine and Rheumatology Unit, University Hospital of Parma, Italy; [3]Rheumatology Clinic, Centro Specialistico Ortopedico-Traumatologico Gaetano Pini-CTO ASST Gaetano Pini, Milan, Italy; [4]Rheumatology Unit-Azienda Ospedaliera Universitaria Senese, Siena, Italy; [5]Department of Emergency and Organ Transplantation, Rheumatology Unit, University of Bari, Italy; [6]Rheumatology Clinic, Ospedale Carlo Urbani, Università Politecnica delle Marche, Jesi (AN), Italy; [7]Rheumatology Unit, Azienda Ospedaliera San Camillo-Forlanini, Rome, Italy; [8]Rheumatology Section, Department of Medical Sciences, University of Ferrara, Italy; [9]Rheumatology Unit, Azienda Ospedaliera Città della Salute e della Scienza di Torino, Turin, Italy

11	The accuracy of intra-articular injection depends on the joint and on the skills of the practitioner. Ultrasound-guidance may improve accuracy and it is particularly recommended for joints that are difficult to access due to the site itself, degree of deformity or obesity. *Hyaluronic Acid:* intra-articular injection of hyaluronic acid of different molecular weights may give symptomatic benefit with low toxicity and could help to reduce the NSAID use. Steroids: intra-articular corticosteroid injection may be beneficial, providing fast pain relief in patients who suffer painful relapses and who do not respond or have a contraindication to analgesics and NSAIDs. *Mesenchymal stem cells and/or platelet rich plasma:* It is unclear if intra-articular injection of mesenchymal stem cells or platelet-rich plasma can help to relieve pain associated with knee OA.	1-5

Reumatismo, 2019; 71 (S1): 22-49

The Italian Society for Rheumatology clinical practice guidelines for rheumatoid arthritis

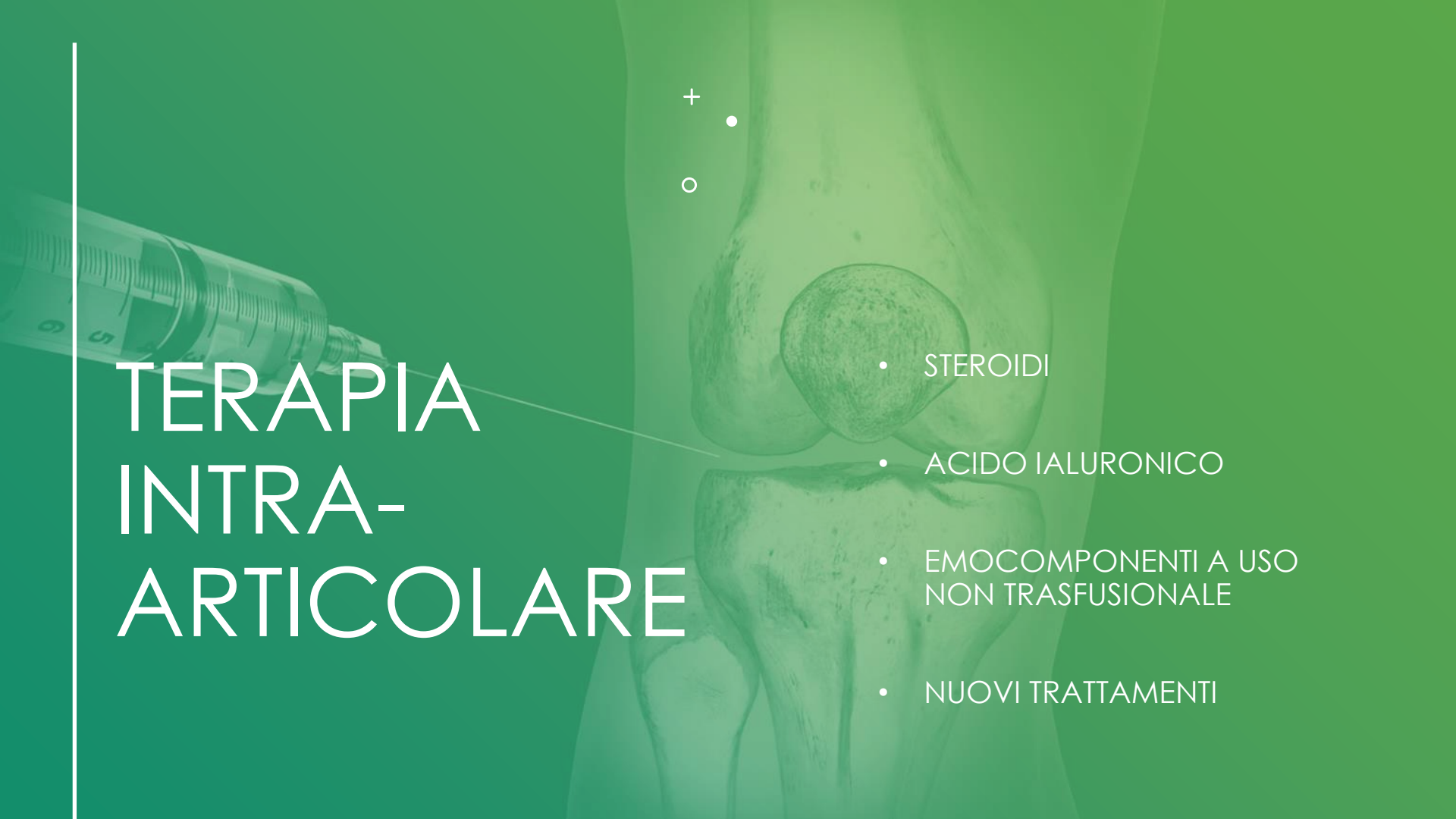
S. Parisi[1,2], A. Bortoluzzi[1,3], G.D. Sebastiani[4], F. Conti[5], R. Caporali[6], N. Ughi[1,7], I. Prevete[1,4], A. Ariani[1,8], M. Manara[1,7], G. Carrara[1], C.A. Scirè[1,3]

[1]Epidemiology Research Unit, Italian Society for Rheumatology, Milan, Italy; [2]Rheumatology Unit, University Hospital, Turin, Italy; [3]Department of Medical Sciences, Rheumatology Section, University of Ferrara, Italy; [4]Rheumatology Unit, Azienda Ospedaliera San Camillo-Forlanini, Rome, Italy; [5]Rheumatology Division, I Clinica Medica, Policlinico Umberto I, Rome, Italy; [6]Department of Rheumatology, University and IRCCS Foundation Policlinico S. Matteo, Pavia, Italy; [7]Division of Clinical Rheumatology, Centro Specialistico Ortopedico-Traumatologico Gaetano Pini CTO ASST, Milan, Italy; [8]Department of Medicine, Internal Medicine and Rheumatology Unit, Azienda Ospedaliero-Universitaria di Parma, Italy

Table VI - Final set of Recommendations on treatment strategy in RA (Management).

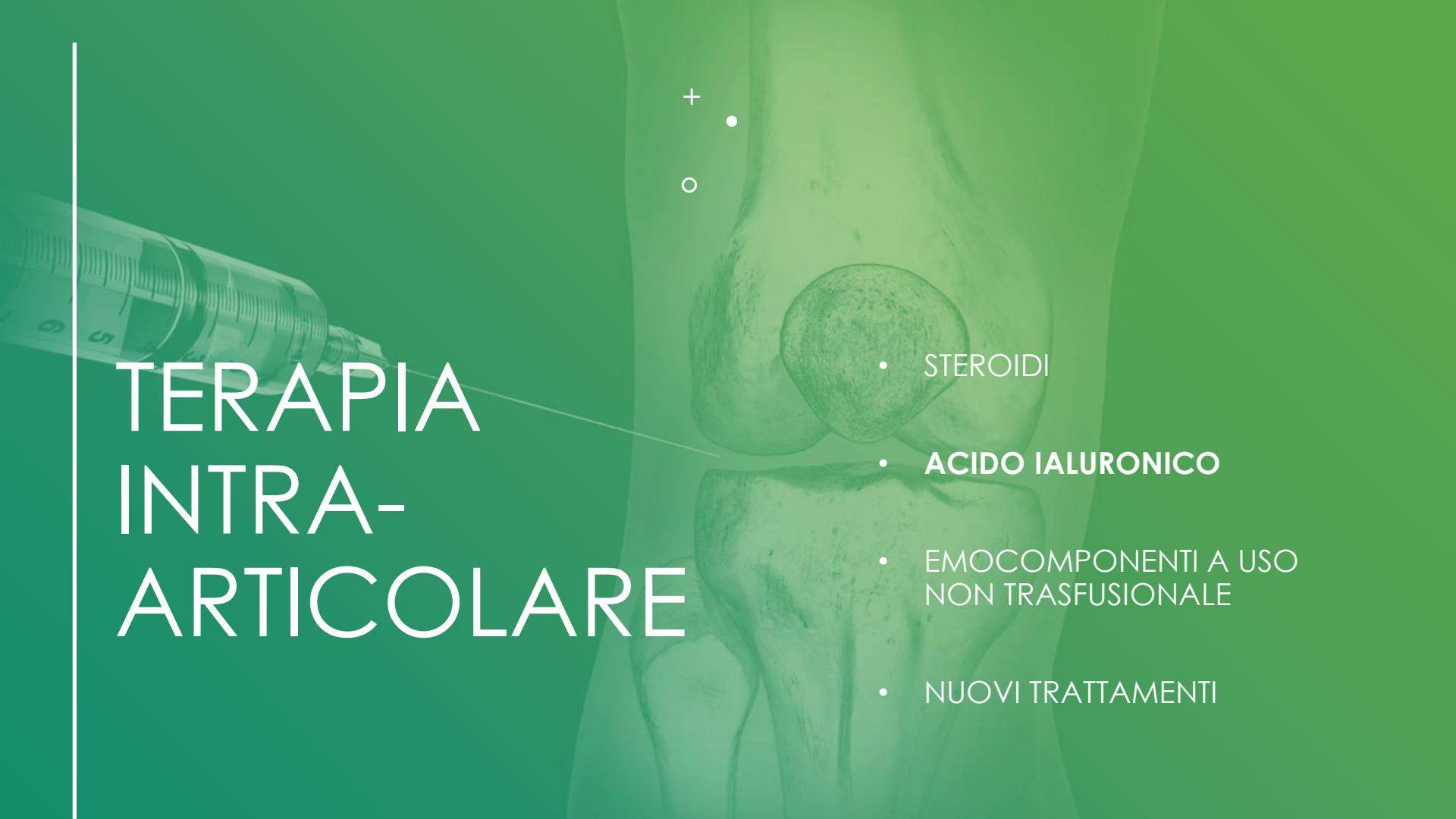
No.	The final set of "Management" Recommendations	Category of Evidence	Grade of Recommendation
1	Treatment with csDMARDs should be started as soon as the diagnosis of RA is made.	1	A
2	MTX should be part of the first treatment strategy.	1	A
3	Short-term course of glucocorticoids can be considered to control active RA in combination with csDMARDs. In view of their cumulative side effects, they should be used at the lowest dose necessary and tapered as rapidly as clinically feasible (<3 months). Intra-articular glucocorticoid injections should be considered for the relief of local symptoms of inflammation.	1	A

TERAPIA INTRA-ARTICOLARE



- STEROIDI
- ACIDO IALURONICO
- EMOCOMPONENTI A USO NON TRASFUSIONALE
- NUOVI TRATTAMENTI

TERAPIA INTRA-ARTICOLARE



- STEROIDI
- **ACIDO IALURONICO**
- EMOCOMPONENTI A USO NON TRASFUSIONALE
- NUOVI TRATTAMENTI

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

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

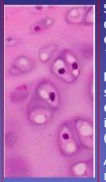
Effetti biologici dell'AI

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

Sulla matrice extracellulare

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

Aumentata sintesi di condroitinsolfato (Kawasaki et al. 1999)

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Sulla cartilagine

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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)

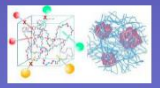
Riduzione espressione IL-1α e stromelisina e produzione NO (Takahashi et al. 1999, 2001, Kobayashi et al. 2004)

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

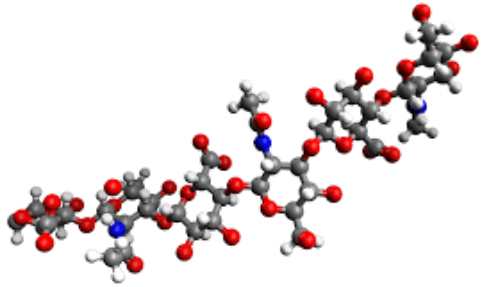
Sulle cellule immunitarie

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

Soppressione adesione ed aggregazione neutrofila (Forrester & Lackie 1981)



HA in commercio



La maggior parte degli HA commerciali ha struttura analoga a quello endogeno a parte quelli ad alto peso molecolare che presentano 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).

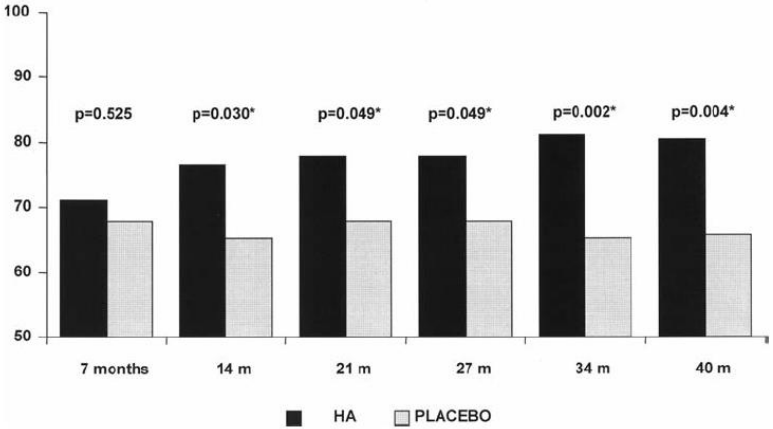
Table 1 Preparations of intra-articular hyaluronic acid (HA) and hylan available in Europe and/or the USA

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	
Erectus®	NA	NA	NA	
Euflexxa®	20 mg/2 ml	Sodium hyaluronate	Biofermentation	
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 co avian)	500–730
Hyalgan®	20 mg/2 ml	Sodium hyaluronate	Roo ian)	500–730
Hyalubrix®	30 mg/2 ml	Sodium hyaluronate		1,500
Intragel® 0.8%	16 mg/2 ml	Sodium hyaluronate	ntation	1,200
Intragel® 1.6%	32 mg/2 ml			
Jointex®	16 mg/2 ml	Sodium hyaluronate	rmentation	
Jointex® Starter	32 mg/2 ml			
MonoVisc®	20 mg/ml	Sodium hyaluronate		
NeoVisc®	20 mg/2 ml	Sodium hyaluronate		1,000
Orthovisc®	30 mg/2 ml	High molecular weight hyaluronan	chemical mo	1,100–2,900
Orthovisc® mini	15 mg/1 ml			1,450
Ostenil®	20 mg/2 ml	Sodium hyaluronate		1,200
Ostenil® mini	10 mg/ml			
RenehaVis®	7 mg/0.7 ml +			1,000
	15.4 mg/0.7 ml			2,000
Sinovial®	16 mg/2 ml		Biofermentation	800–1,200
Sinovial® Mini	8 mg/1 ml			
Sinovial® Forte	32 mg/2 ml			
SportVis®	12 mg/1.2 ml +	Sodium hyaluronate	Biofermentation	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 hyaluro	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			

Antonio Gigante · Leonardo Callegari
Rheumatol Int (2011) 31:427–444

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

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

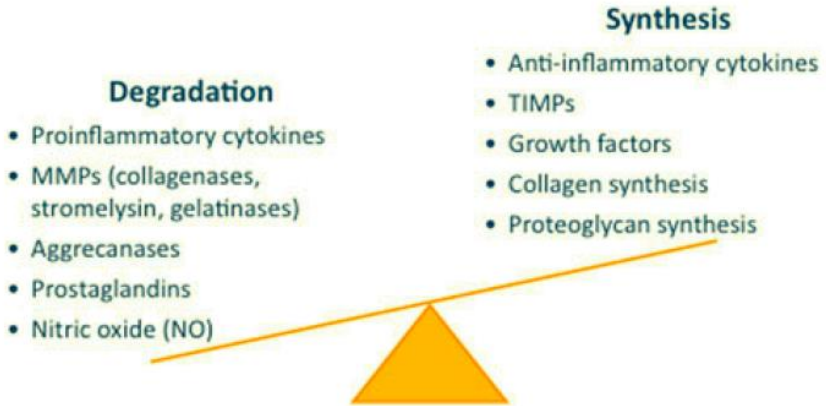
Figure 3 Evolution of responders Osteoarthritis Research Society International, 2004. HA, hyaluronic acid.

Eur J Orthop Surg Traumatol (2013) 23:119–124
DOI 10.1007/s00590-012-0940-0

GENERAL REVIEW

Viscosupplementation with hyaluronic acid in the treatment for cartilage lesions: a review of current evidence and future directions

Travis E. Clegg · David Caborn · Cyril Mauffre



Recent literature supports the use of **HA not only in the management of the pain** associated with osteoarthritis but **also as a disease-modifying agent** as well. Further studies have started to define exciting new roles for viscosupplementation in the treatment for acute injuries to the joint microenvironment.

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]

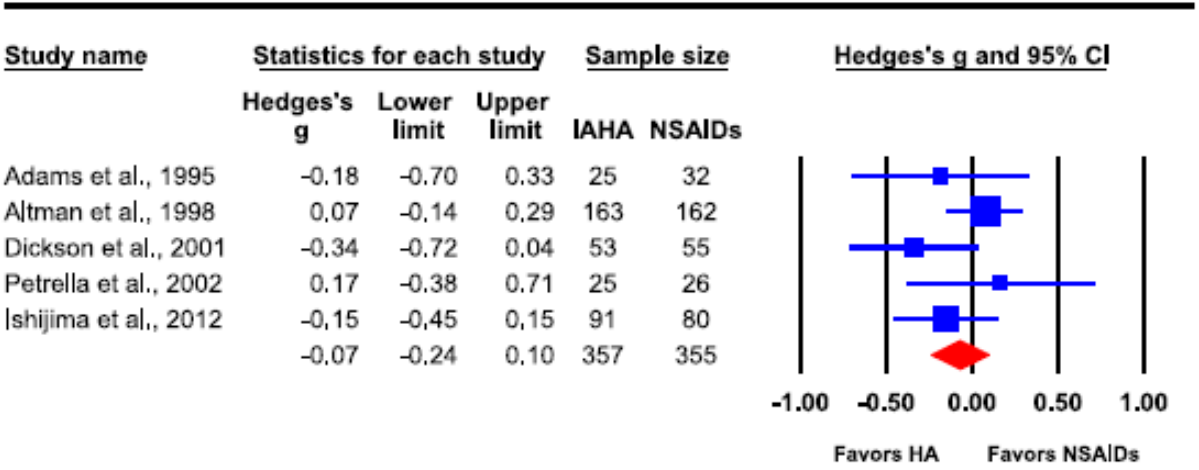
[a] *Center for Treatment Comparison and Integrative Analysis (CTCIA), Tufts Medical Center, 800 Washington St. #63, Boston, MA 02111*
[b] *Division of Rheumatology, Tufts Medical Center, Boston, MA*

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.

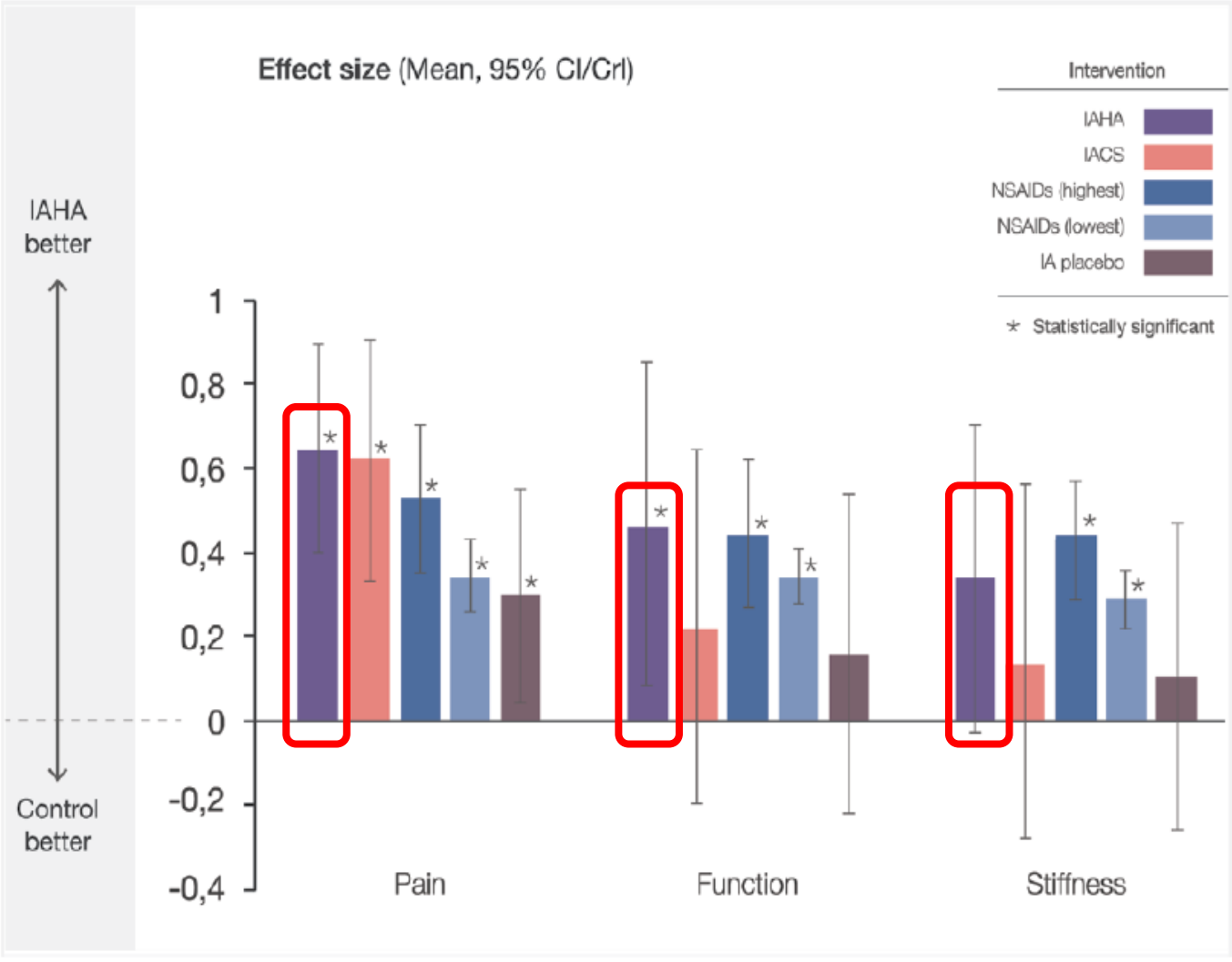
Conclusion

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.

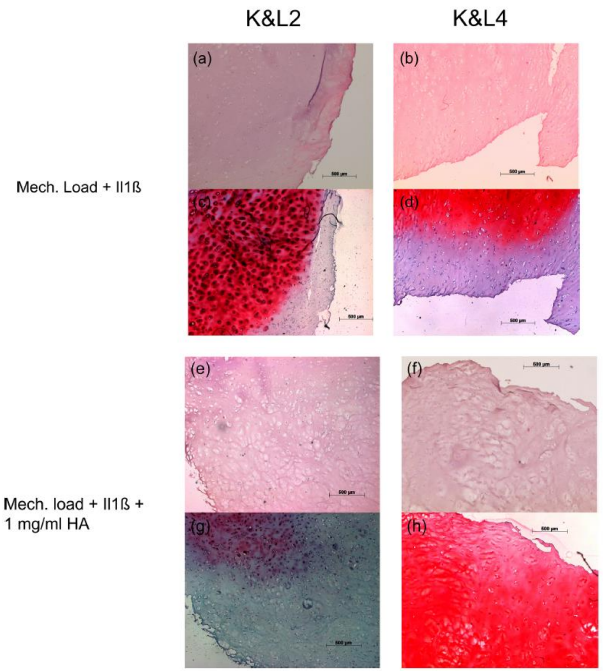
Therapeutic Advances in Musculoskeletal Disease

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


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

PLOS ONE



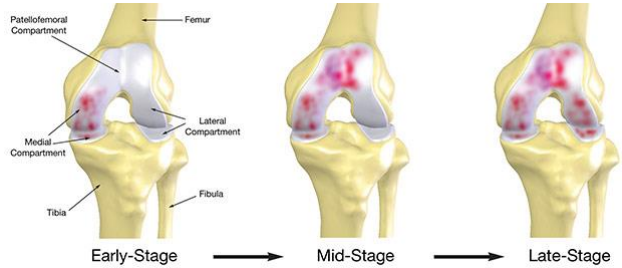
RESEARCH ARTICLE

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

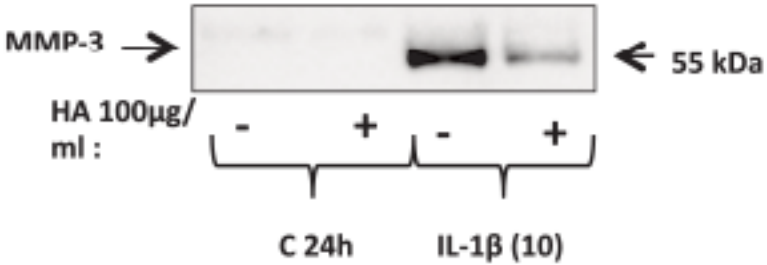


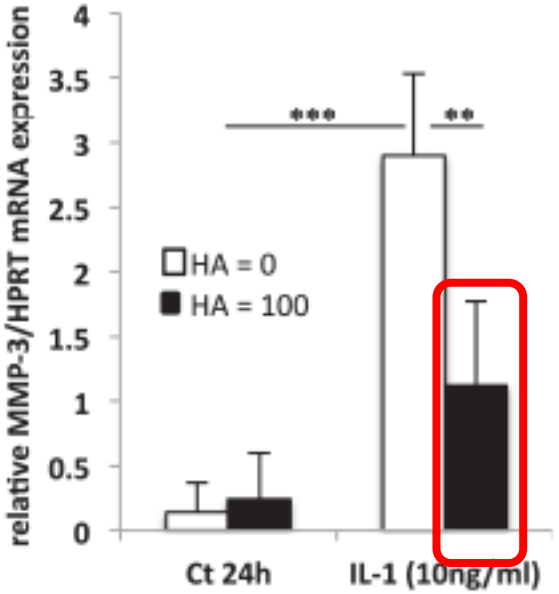
The Journal of Rheumatology

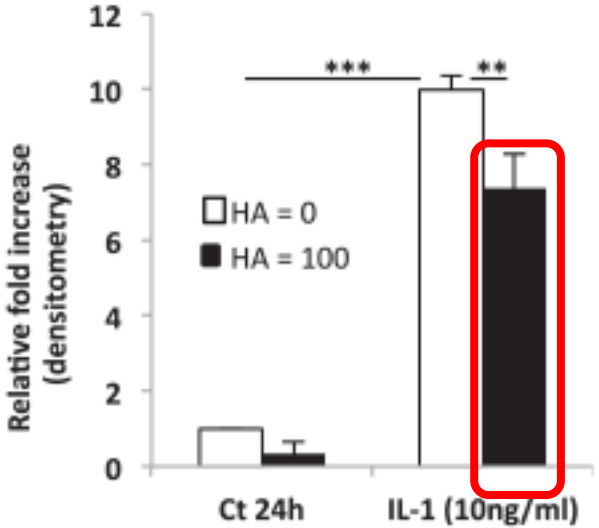
The Journal of Rheumatology Volume 41, no. 5

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







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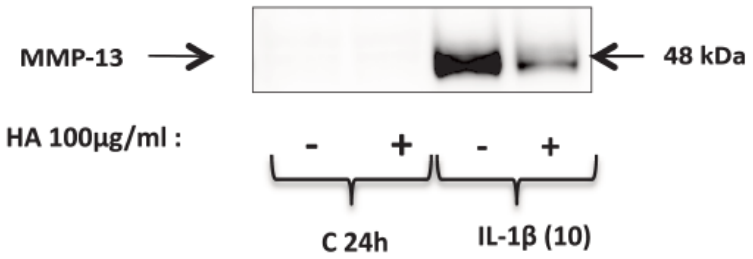
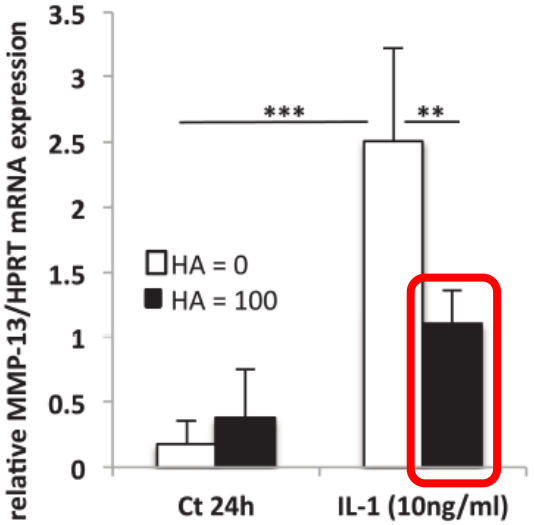
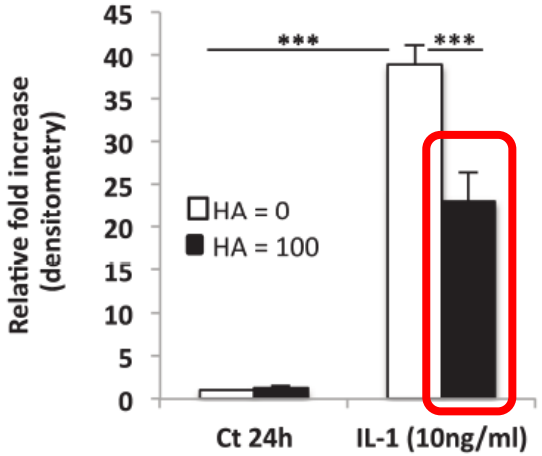






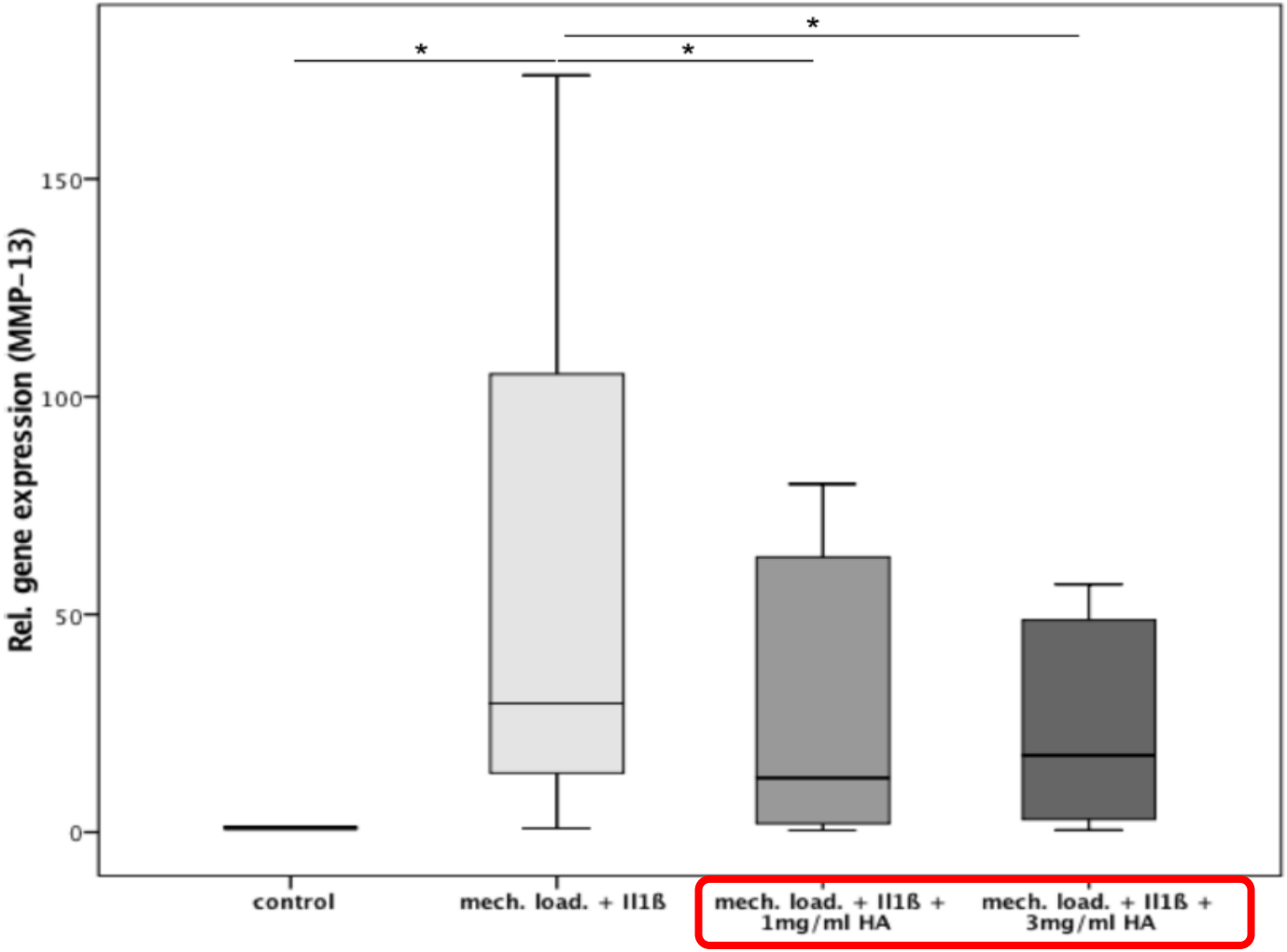


Fig 2. Relative gene expression of MMP-13 in the 3 study groups: (1) 2ng/ml IL1ß + mechanical loading, (2) 2ng/ml IL1ß + mechanical loading + 1mg/ml HA, (3) 2ng/ml IL1ß + mechanical loading + 3mg/ml HA and the control; * indicates statistical significance with p<0,05.

Online version at http://www.minervamedica.it

Minerva Medica 2019 mese;110(0):000–000
DOI: 10.23736/S0026-4806.19.06190-1

ORIGINAL ARTICLE

Ultrasound-guided intra-articular injection: efficacy of hyaluronic acid compared to glucocorticoid in the treatment of knee osteoarthritis

Simone PARISI *, Maria C. DITTO, Marta PRIORA, Richard BORRELLI, Angela LAGANÀ, Clara L. PERONI, Enrico FUSARO

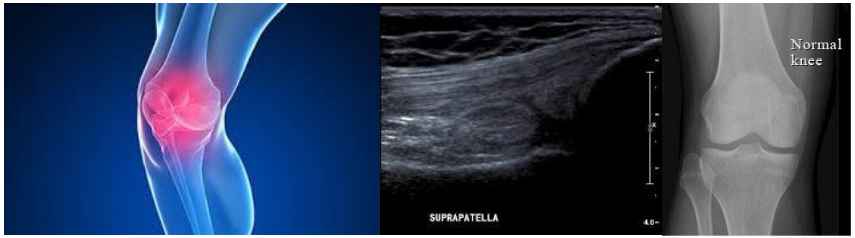


Figure 1

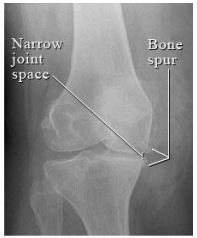
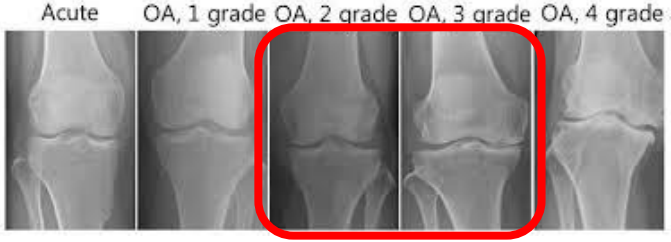
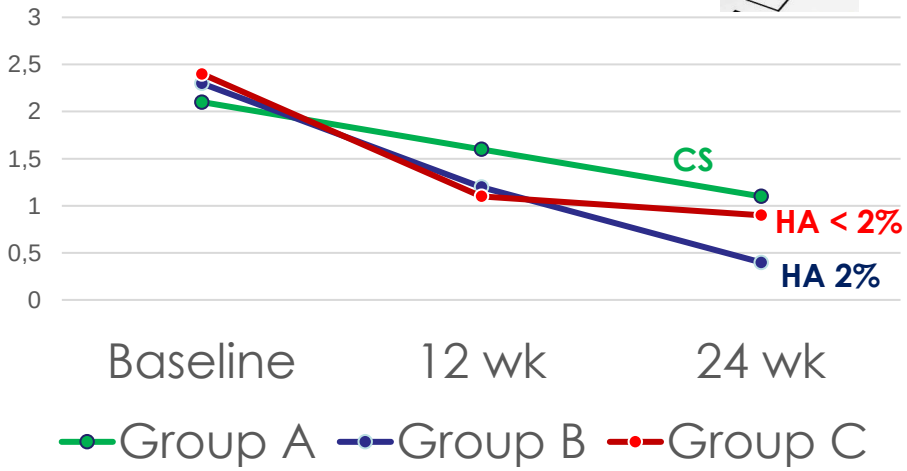


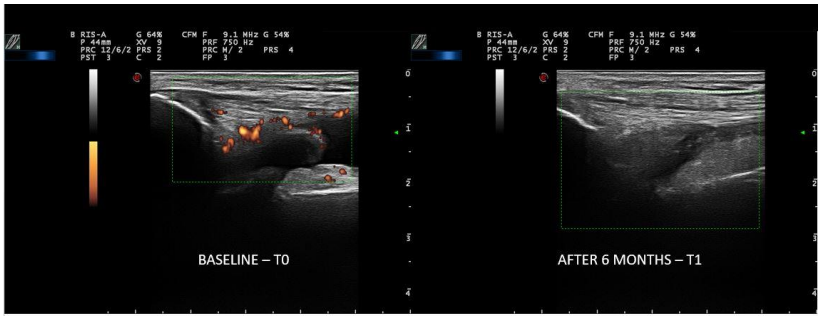
Figure 2

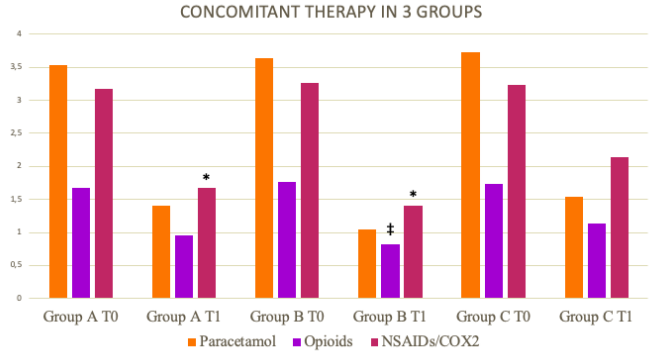
RESULTS



US PWD







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)

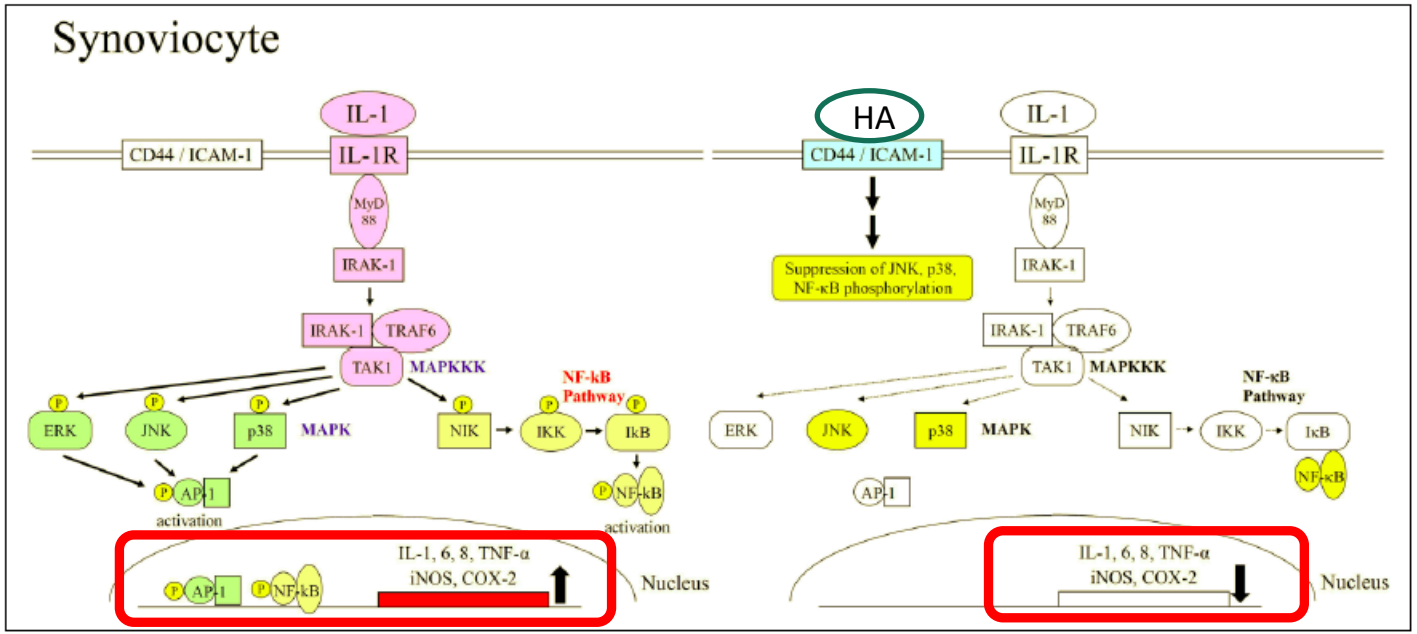


Figure 2. Upregulation of inflammatory gene expressions by IL-1 and the molecular mechanism of its downregulation by Supartz FX in synoviocytes. The binding of IL-1 to its receptor on cell surface activates MAP kinase and NF-κB signal transductions in synoviocytes. These signal transductions induce activation 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.

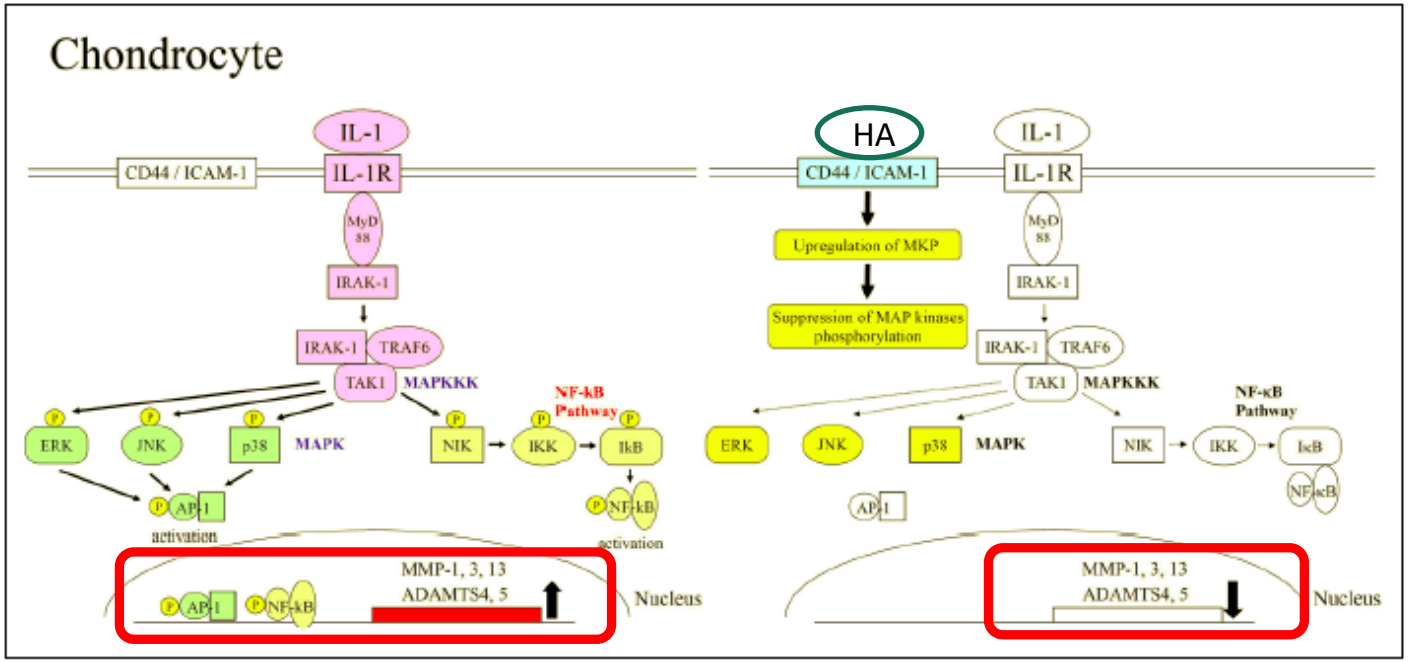
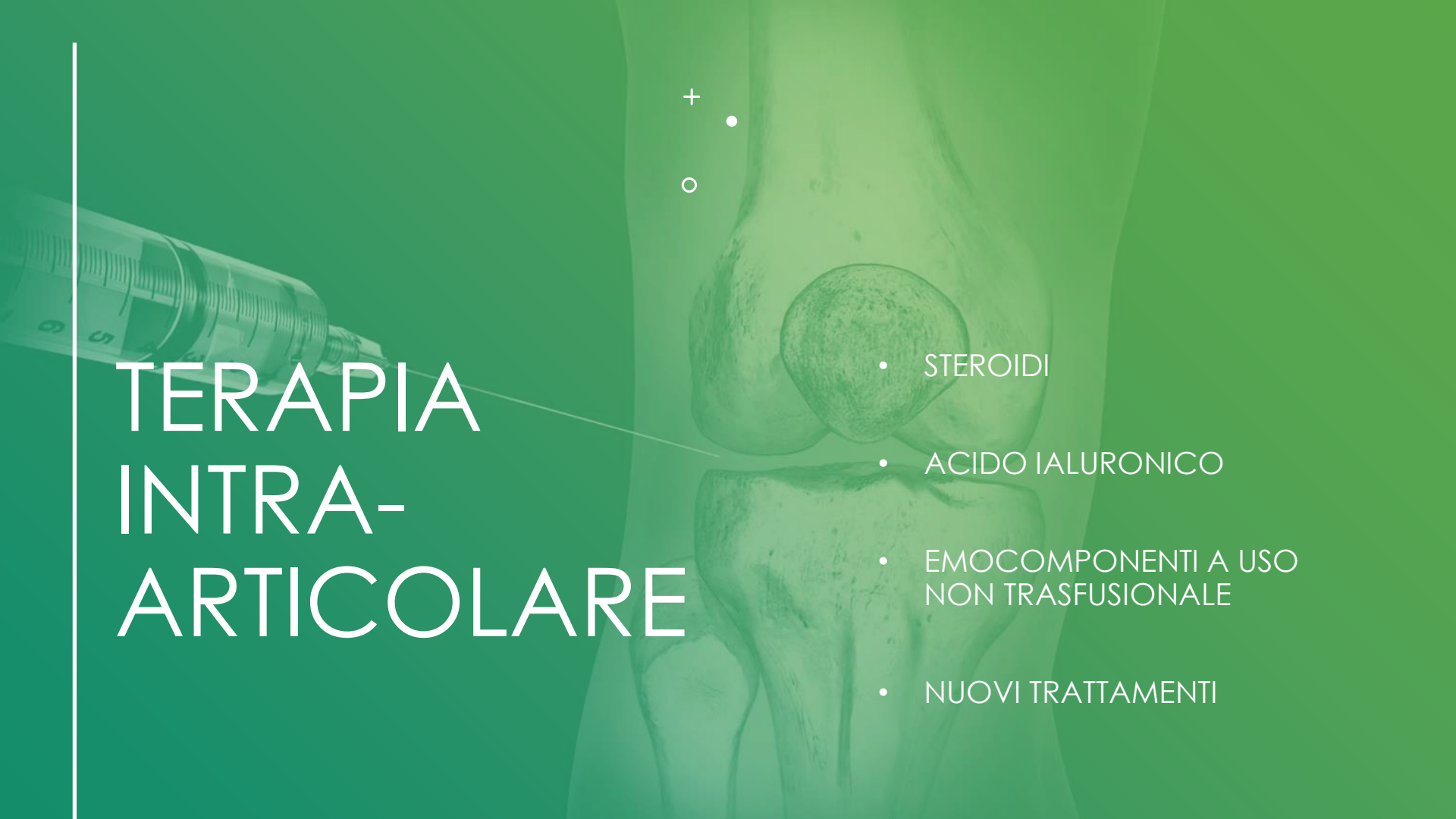


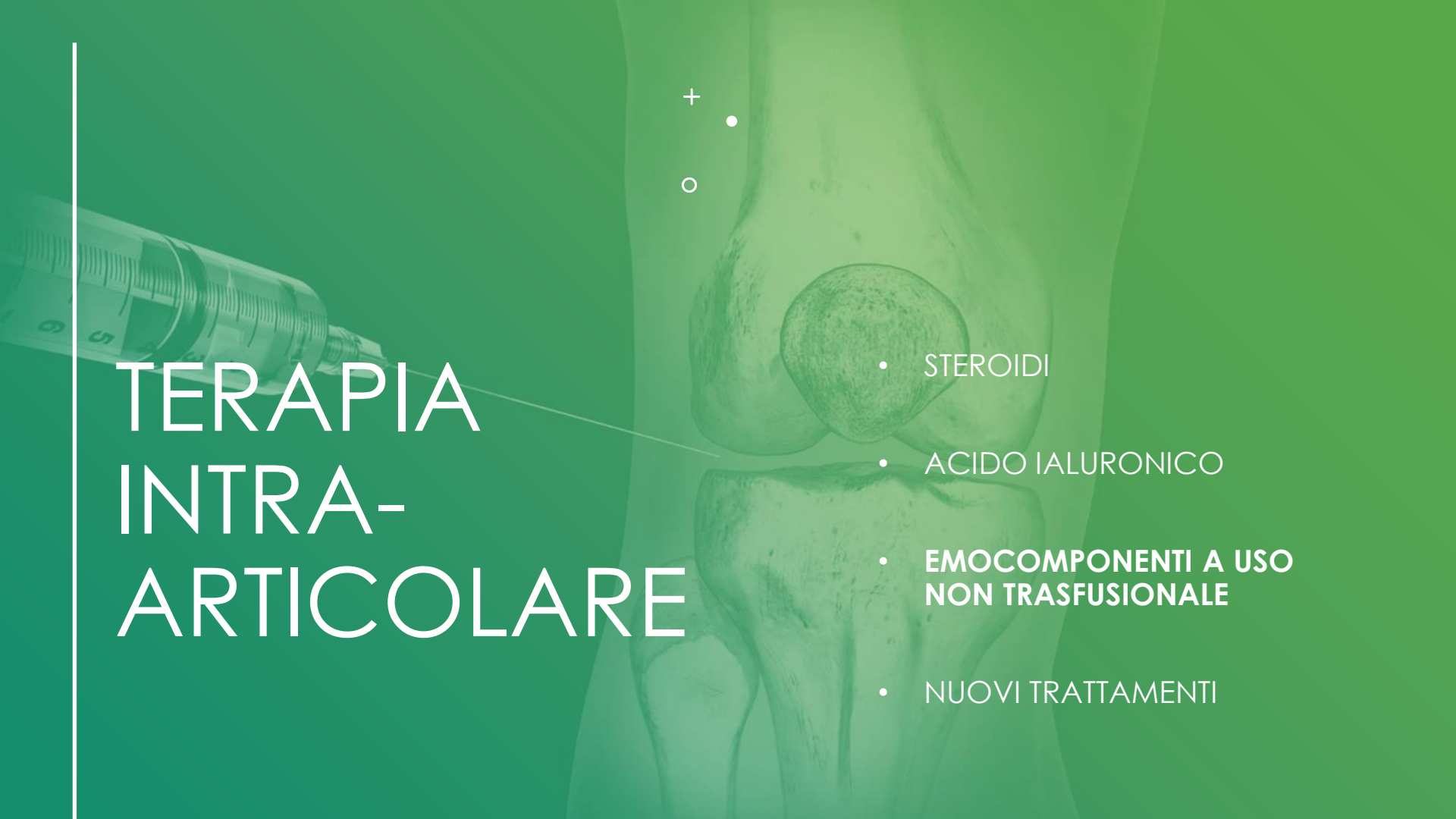
Figure 3. Upregulation of MMP and ADAMTS gene expressions by IL-1 and the molecular mechanism of its downregulation by Supartz FX in chondrocytes. As in synoviocytes, the binding of IL-1 to its receptor activates MAP kinase and NF-κB signal transductions in chondrocytes. These signal transductions induce 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.

TERAPIA INTRA-ARTICOLARE



- STEROIDI
- ACIDO IALURONICO
- EMOCOMPONENTI A USO NON TRASFUSIONALE
- NUOVI TRATTAMENTI

TERAPIA INTRA-ARTICOLARE



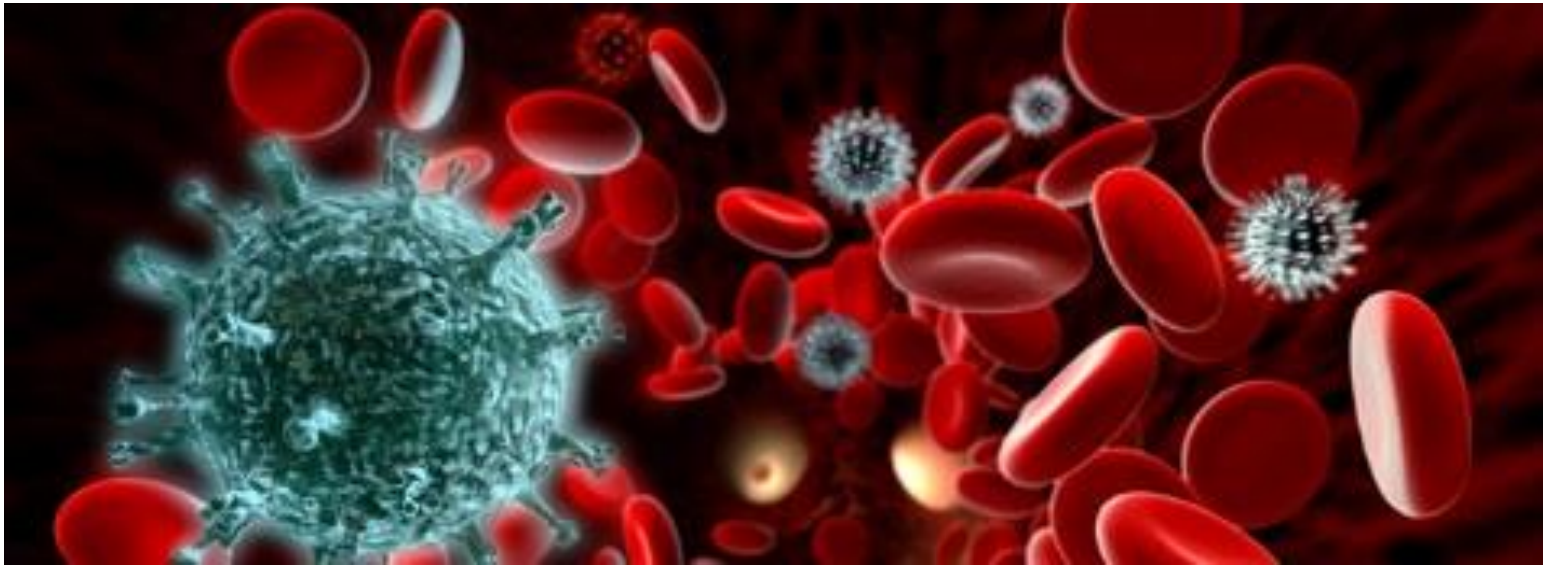
- STEROIDI
- ACIDO IALURONICO
- **EMOCOMPONENTI A USO NON TRASFUSIONALE**
- NUOVI TRATTAMENTI

Platelet rich plasma (PRP) è una nuova terapia di natura autologa che sta fortemente emergendo negli ultimi anni per il successo terapeutico riscontrato in alcuni "Super Atleti"
Calciatori, Tiger Woods e Rafael Nadal hanno attribuito , in parte, il loro "recupero miracoloso" all'utilizzo di questo "*enigmatico trattamento*"

Dal 2000

"PRP phenomenon"

De La Mata Rheumatol Clin 2003



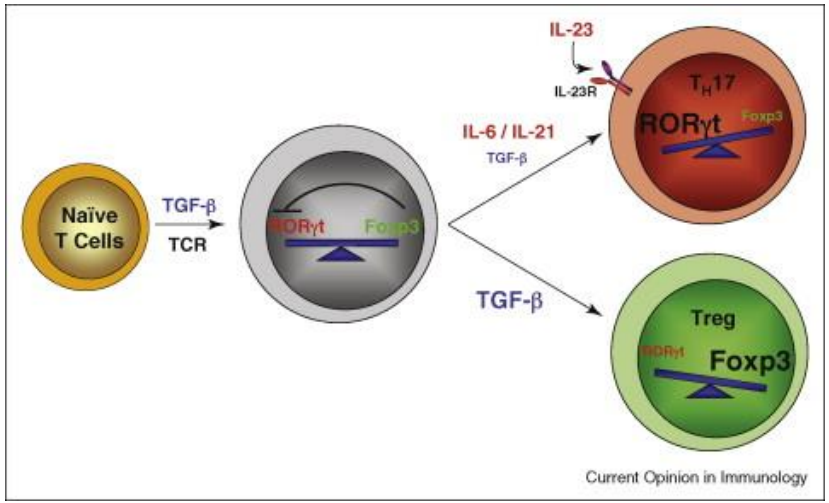
The scientific base of the PRP treatment is based on factors that contrast the immunity pro inflammatory answer and factors that stimulate muscleskeletal cells.

McCarrel T, Fortier L (2009) Temporal growth factor release from platelet-rich plasma, trehalose lyophilized platelets, and bone marrow aspirate and their effect on tendon and ligament gene expression. J Orthop Res 27(8):1033–1042. doi:10.1002/jor.20853

INIEZIONE DI CONCENTRATO PIASTRINICO - PRP

Razionale:

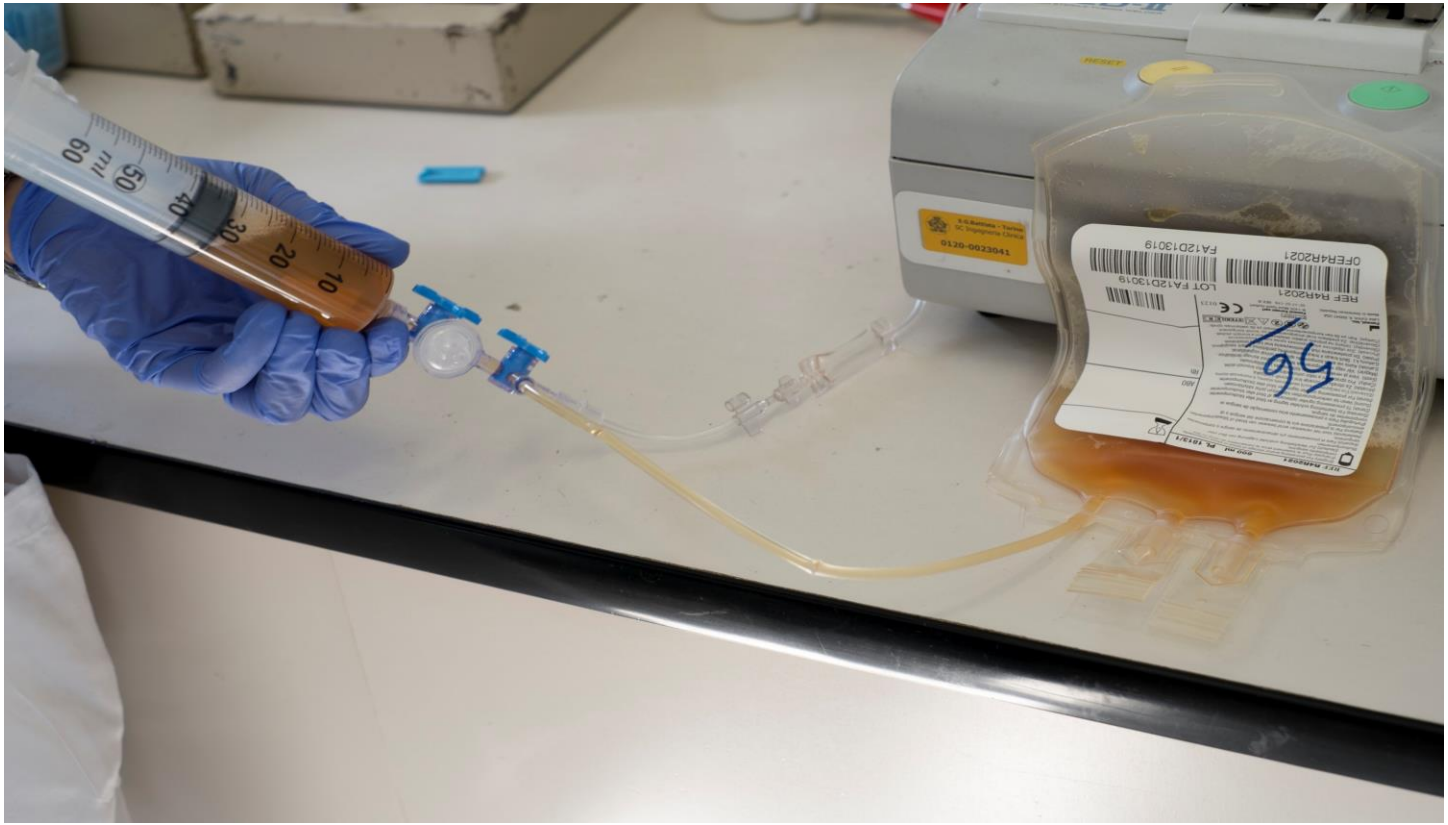
- Preparato ricco in Grow Factors che incentivano i processi riparativi tissutali
- **TGFbeta** è associato a condrogensi nei processi di riparazione cartilaginea
- Aumenta la concentrazione di acido ialuronico



Sampson et al del 2010 Am J. Phys Med Rehabil

TARGET DELL' EC

- Osteoartrosi
- Tendinopatie
- Reumatismi Infiammatori?


60
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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.

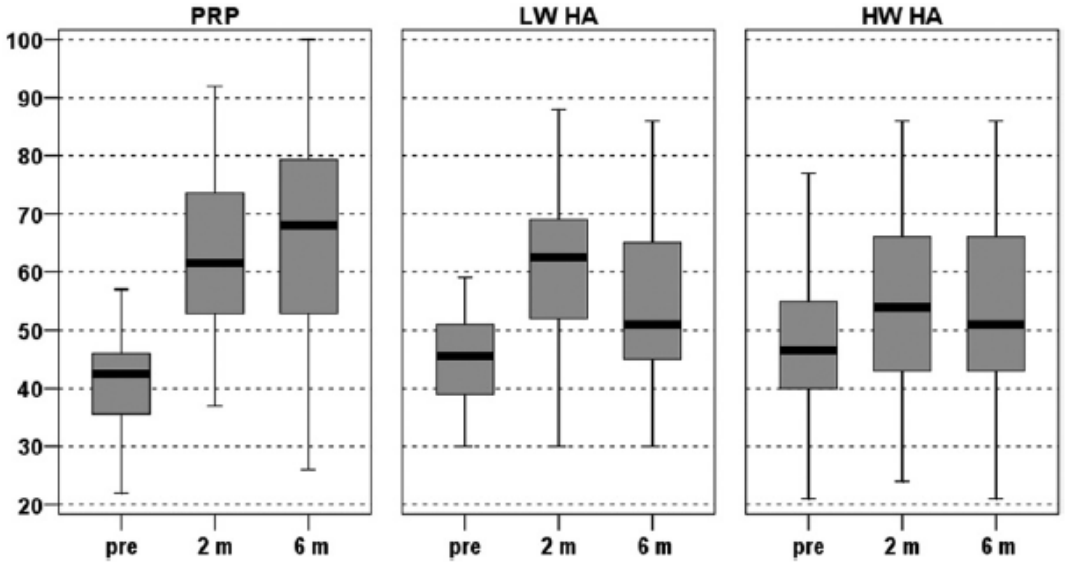
Arthroscopy: The Journal of Arthroscopic and Related Surgery, Vol 27, No 11 (November), 2011: pp 1490-1501

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

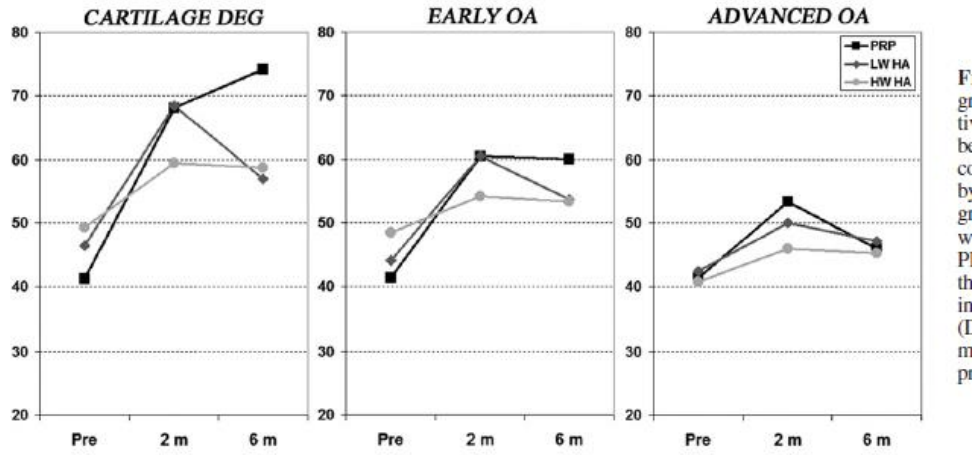
	PRP	LW HA	HW HA	
Age (yr)	50.6 ± 13.8 (30-81)	53.2 ± 13.0 (26-75)	54.9 ± 12.6 (29-76)	NS
Sex	30 M, 20 F	27 M, 23 F	25 M, 25 F	NS
Body mass index (kg/m^2)	24.6 ± 3.2 (18-32)	26.2 ± 2.2 (20-31)	24.8 ± 3.5 (20-35)	$P = .004$
Pathology				NS
Cartilage degeneration	22	19	21	
Early OA	20	22	19	
Advanced OA	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.



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

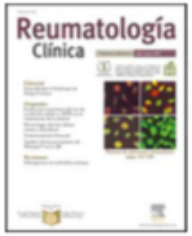
IKDC score (0-100)

Reumatol Clin. 2013;9(3):166–171

ELSEVIER DOYMA

Reumatología Clínica

www.reumatologiaclinica.org



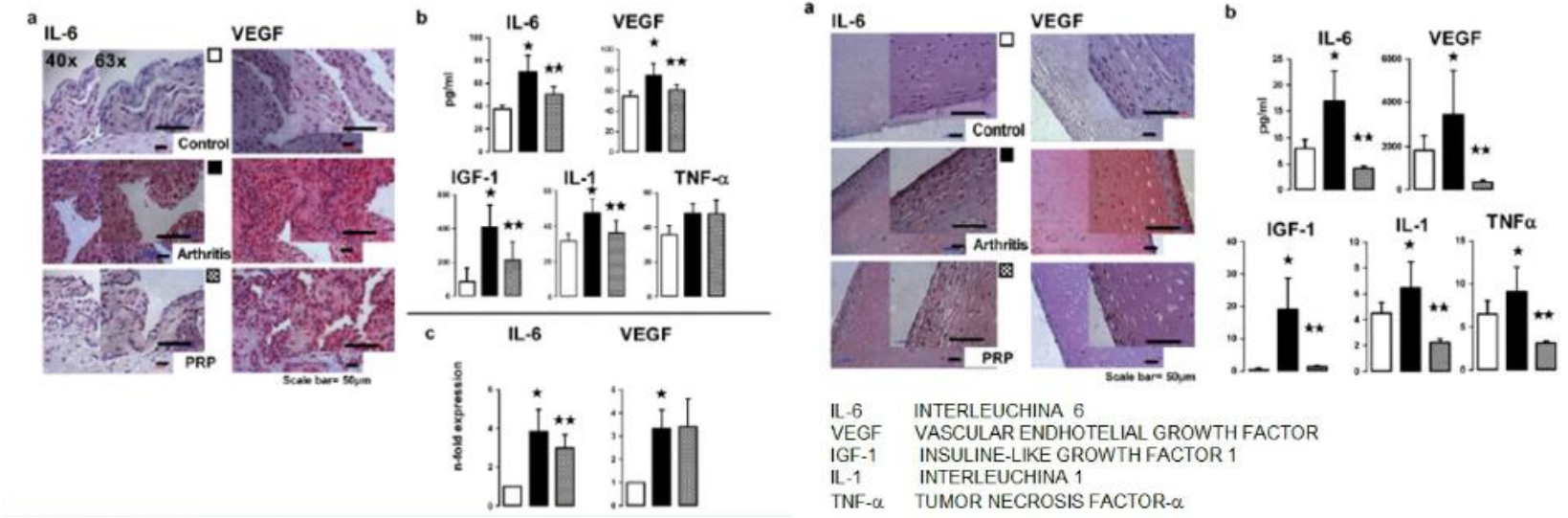
Review Article

Platelet Rich Plasma. A New Treatment Tool for the Rheumatologist?☆

José De La Mata

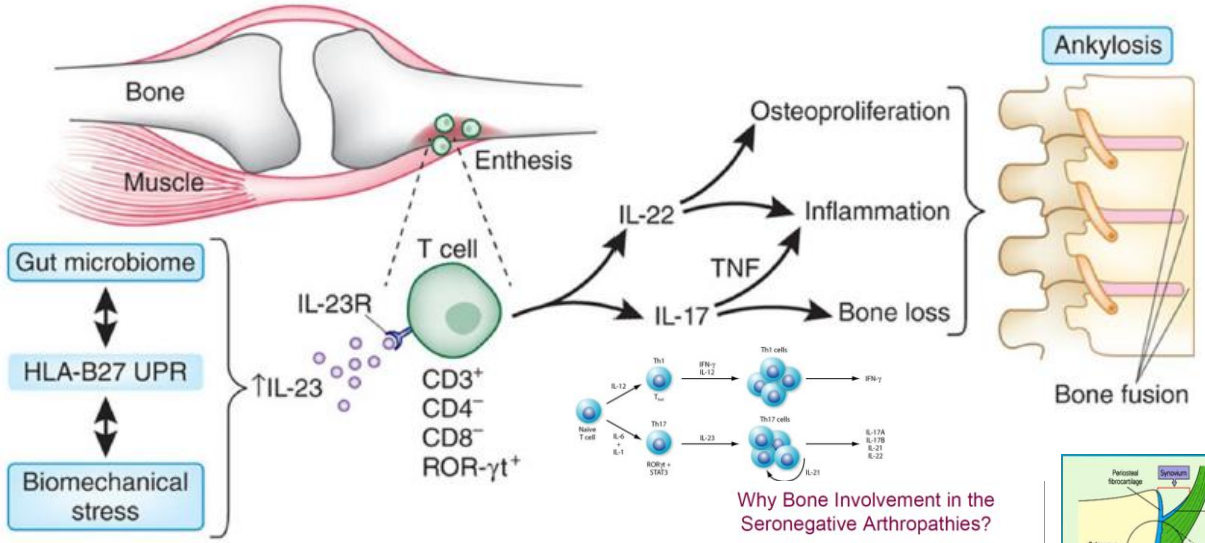
Servicio de Reumatología, Clínica Nuestra Señora del Valle, Madrid, Spain

PRP AND RA



Lippross S et al. Intraarticular Injection of Platelet-Rich Plasma Reduces Inflammation in a Pig Model of Rheumatoid Arthritis of the Knee Joint. ARTHRITIS & RHEUMATISM Vol. 63, No. 11, November 2011, pp 3344–3353 DOI 10.1002/art.30547 © 2011, American College of Rheumatology.

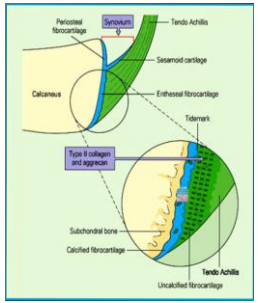
IL-23 and Entheseal-Resident T Cells Promote Enthesitis and Osteoproliferation in Spondyloarthritis



La patogenesi della patologia spondiloartritica vede coinvolte cellule e mediatori del sistema immunitario, come dimostrato sia da studi genetici che immunologici in particolare con riferimento alle cellule T helper Th17

Lories R et al. Nat Med. 2012;18:1018-9 (with permission)

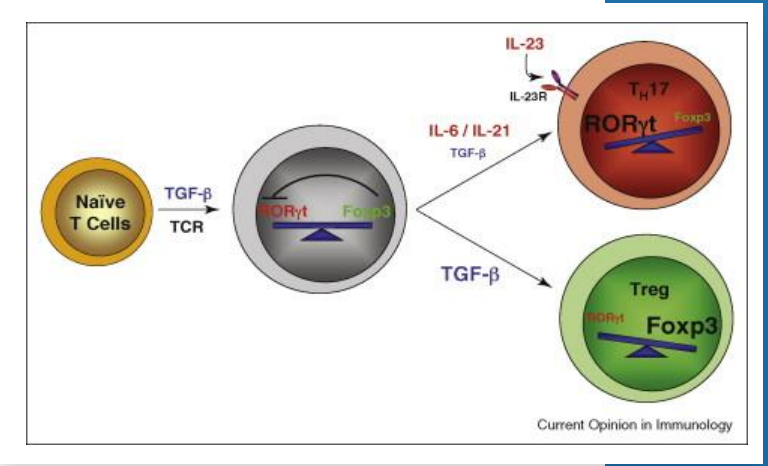
Benjamin et al AR 2007 and Benjamin & McGonagle AR 2007

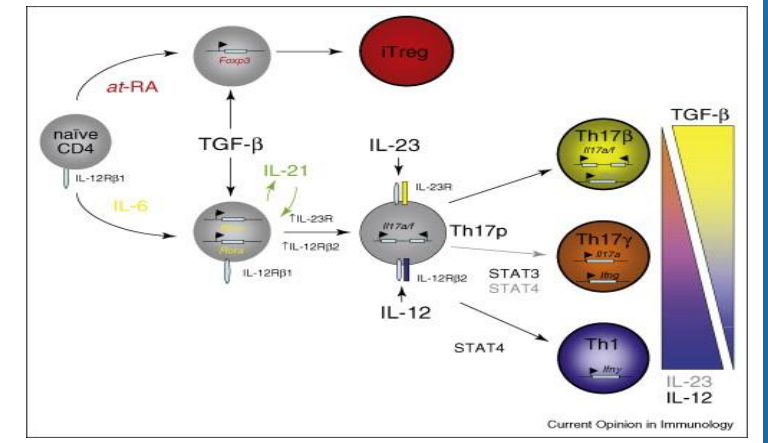


RAZIONALE

- I principi attivi del PRP sono il TGF-beta ed i fattori di crescita quali IGF, il PDGF

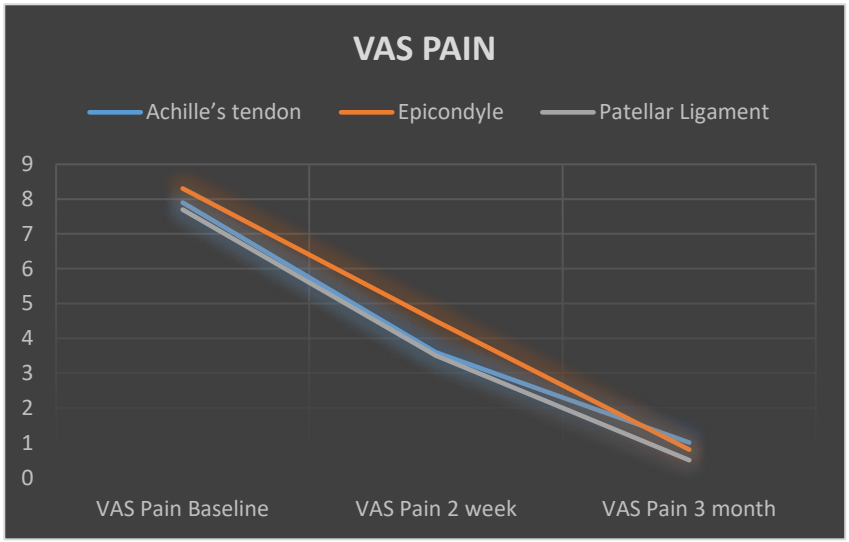
- Il TGF-beta a concentrazioni adeguate inibisce la risposta immune mediata da cellule Th17, contrastandone il priming e convertendo i Tcell naive in T Reg soppressori (Zhou et al, 2008; Crome et al, 2010); il TGFb ha anche la capacità di inibire altre cellule dell'infiammazione, quali altri fenotipi linfocitari e macrofagi, mentre i fattori di crescita piastrinici, per contro, stimolano i tenociti a produrre collagene riparando le lesioni tendinee già in essere (Everts et al, 2006).

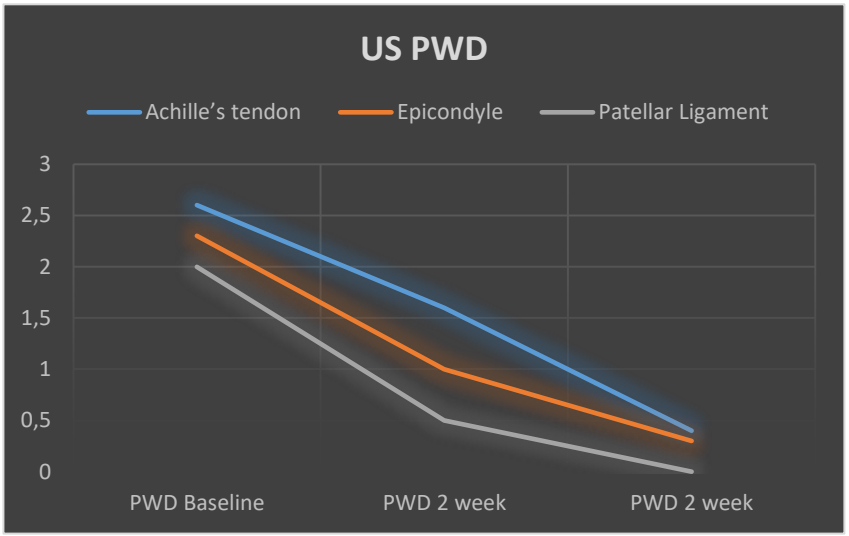




RISULTATI

52pts

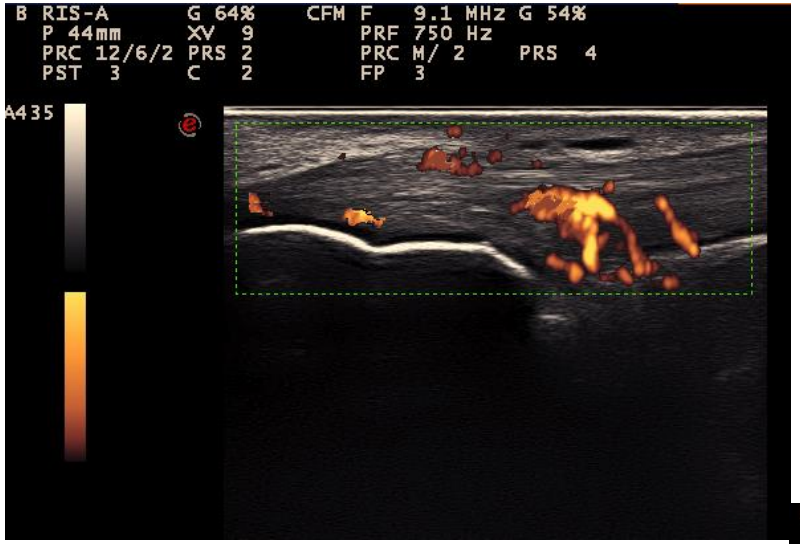




Δ tot VAS PAIN -7.2 p=0,001

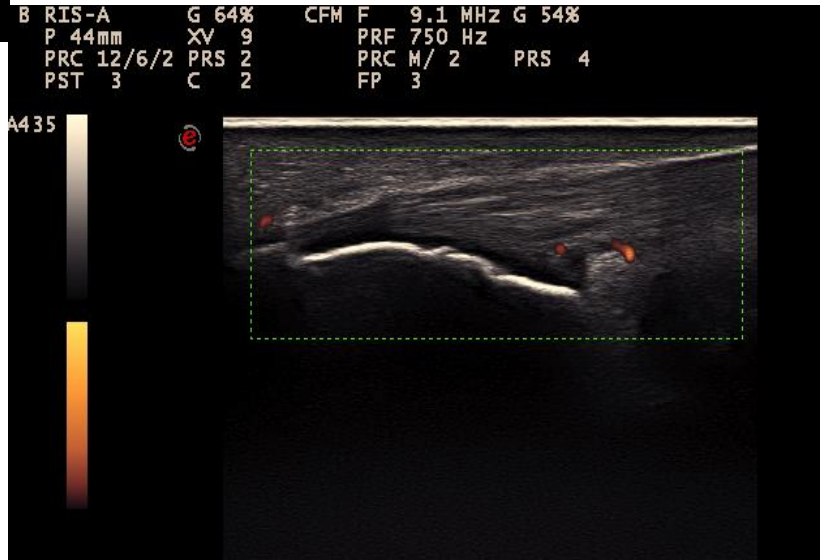
Δ PWD tot -2.1 p=0,008

Submitted Data



PRIMA DEL TRATTAMENTO CON PRP

DOPO TRATTAMENTO CON PRP



www.aging-us.com AGING 2018, Vol. 10, No. 12

Research Paper

Mechanistic insight into hyaluronic acid and platelet-rich plasma-mediated anti-inflammatory and anti-apoptotic activities in osteoarthritic mice

Chi-Sheng Chiou[1,2], Chi-Ming Wu [3], Navneet Kumar Dubey[4,5], Wen-Cheng Lo[6,7], Feng-Chou Tsai[8], Tran Dang Xuan Tung[1,9], Wei-Ching Hung[10], Wei-Che Hsu[10], Wei-Hong Chen[10], Win-Ping Deng[1,10,11]

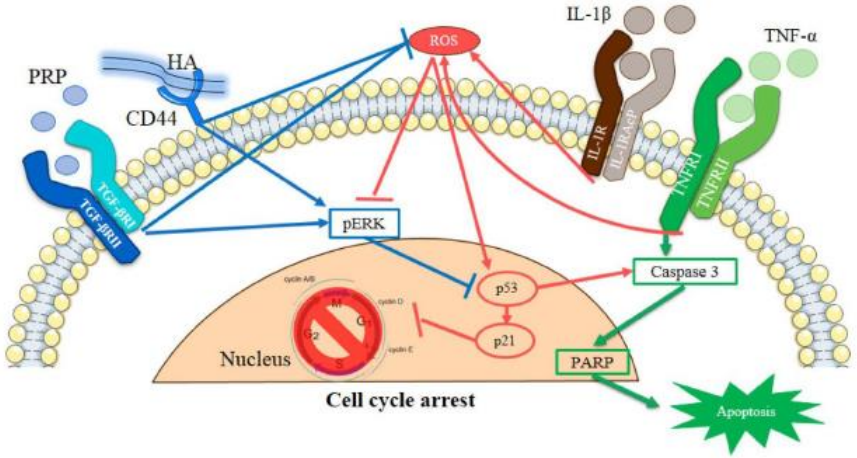


Figure 7. Schematic representation of HA and PRP-mediated cellular apoptosis in osteoarthritic chondrocytes.

SIERO AUTOLOGO CONDIZIONATO

Original papers

Med Ultrason 2018, Vol. 20, no. 3, 335-341
DOI: 10.11152/mu-1495

The efficacy and safety of autologous conditioned serum (ACS) injections compared with betamethasone and placebo injections in the treatment of chronic shoulder joint pain due to supraspinatus tendinopathy: a prospective, randomized, double-blind, controlled study

Nemanja Damjanov[1], Branko Barać[1], Jelena Čolić[1], Vladan Stevanović[2], Ana Zeković[1], Goran Tulić[3]

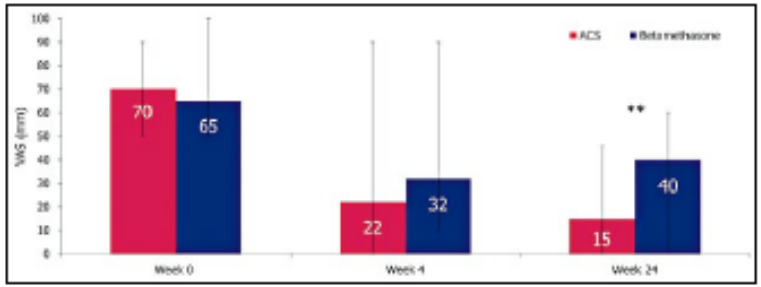
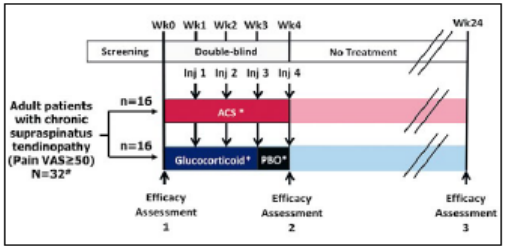


Fig 3. Shoulder pain (VAS) data at weeks 0, 4 and 24. ** Highly significant: p=0.002. VAS: visual analog scale for pain. Median values depicted. Error bars denote minimum and maximum values.



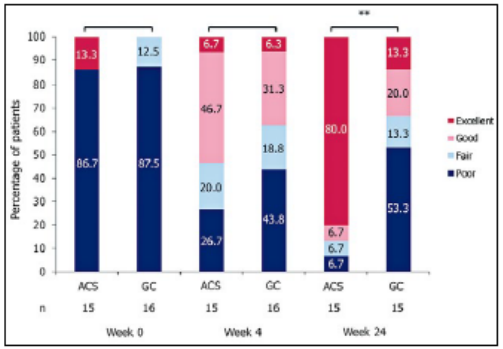
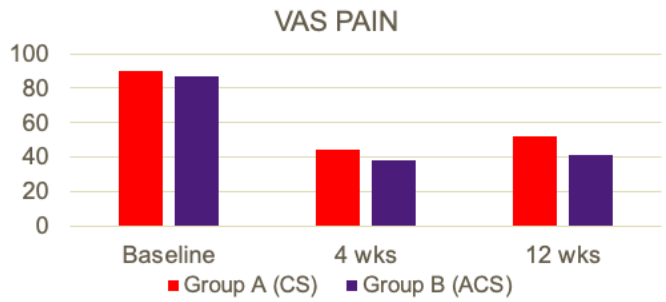


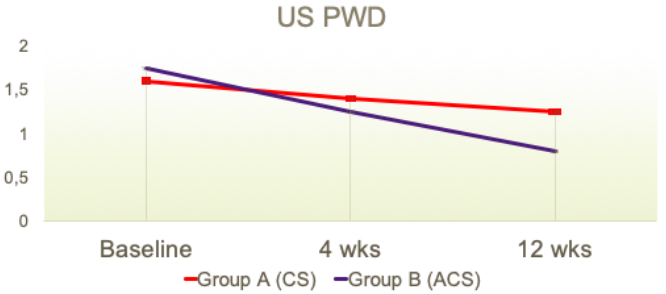
Fig 4. Shoulder function (CSS) data at weeks 0, 4 and 24 of ACS and glucocorticoid-treated patients. ** Highly significant: p<0.002. Full analysis set. CSS: Constant shoulder score. GC: glucocorticoid. CSS scores: <11 is Excellent, 11-20 is Good, 21-30 is Fair and >30 is Poor.

EFFICACY OF AUTOLOGOUS CONDITIONED SERUM IN THE TREATMENT OF KNEE OSTEOARTHRITIS SECONDARY TO RHEUMATOID ARTHRITIS

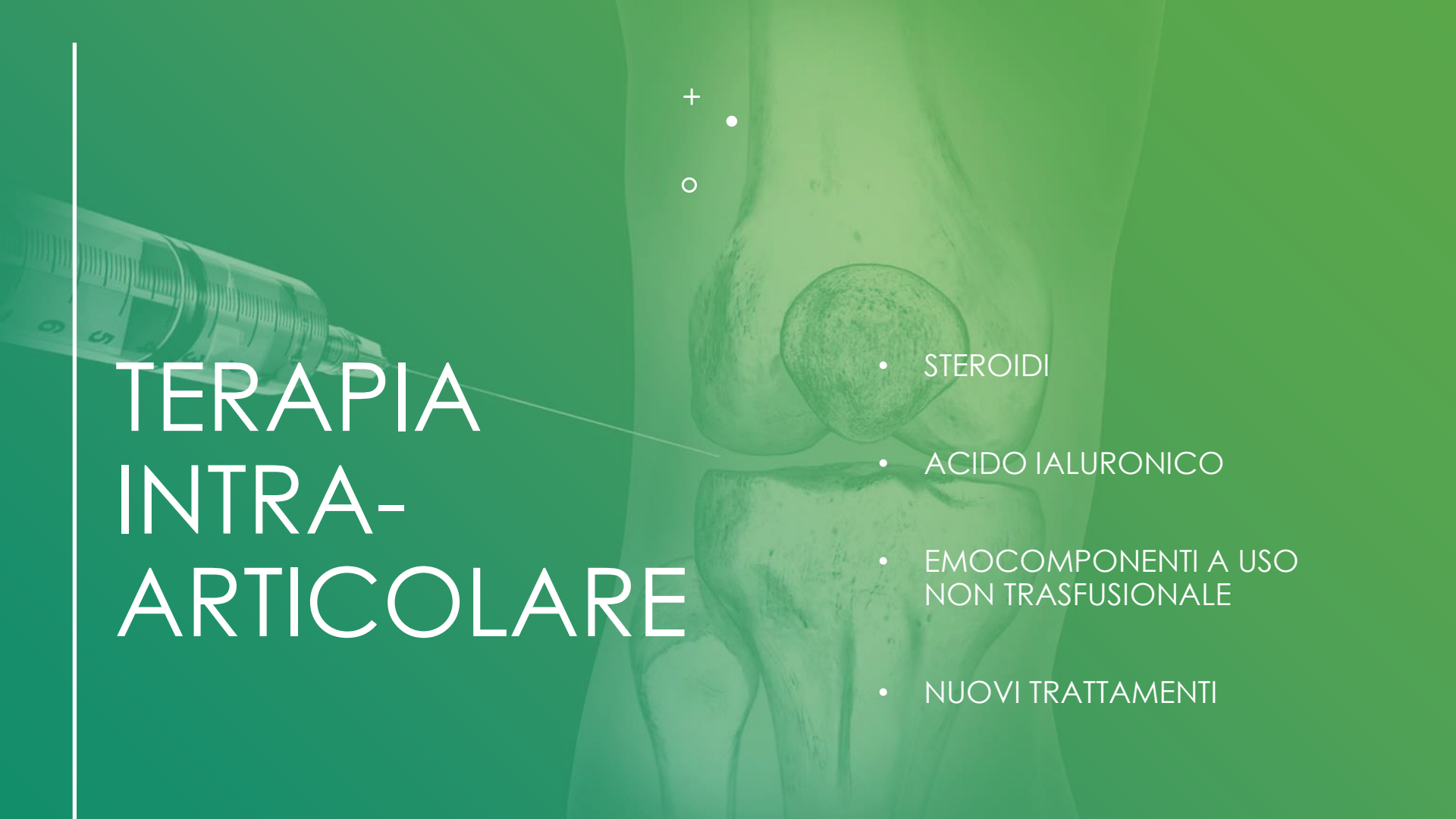
Simone Parisi, Maria Chiara Ditto, Angela Laganà, Clara Lisa Peroni, Sergio D'Antico, Enrico Fusaro
S.C. Reumatologia Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino, Turin, Italy

ACS therapy improved joint function and **reduced** knee **pain** more effective than triamcinolone; combined with its favorable **safety profile**, ACS appears to be a more effective treatment than glucocorticoids and could enhance the quality of life in patients with knee OA in RA. ACS has the potential to offer an alternative, **chondroprotective**, natural, molecular approach to treating pain and functionality in patients with symptomatic knee OA in particular related to RA.



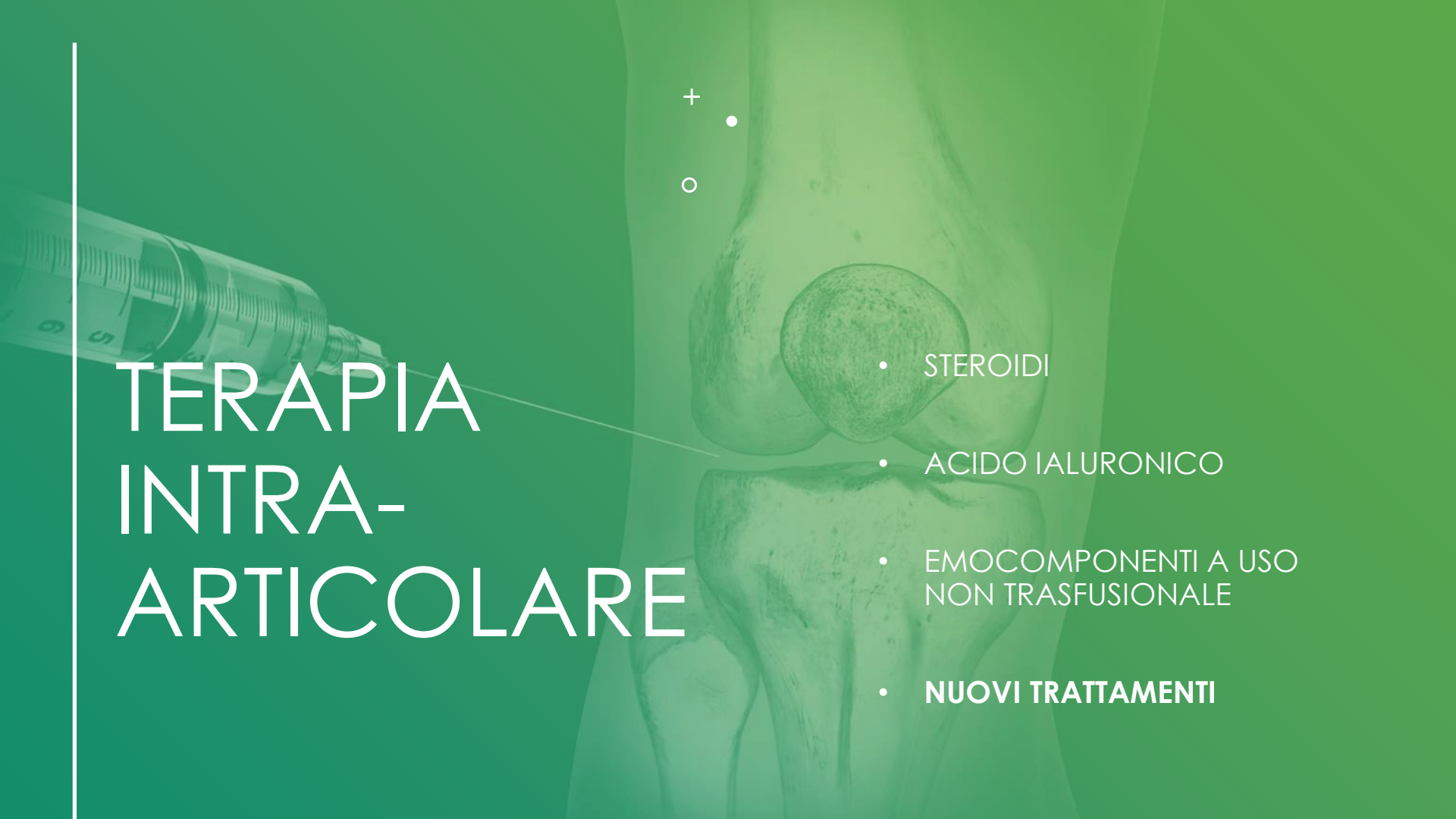


TERAPIA INTRA-ARTICOLARE



- STEROIDI
- ACIDO IALURONICO
- EMOCOMPONENTI A USO NON TRASFUSIONALE
- NUOVI TRATTAMENTI

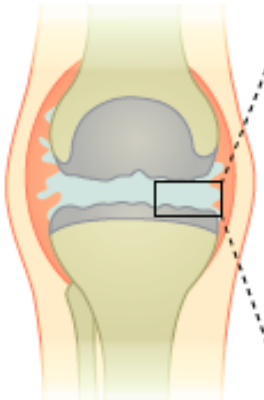
TERAPIA INTRA-ARTICOLARE

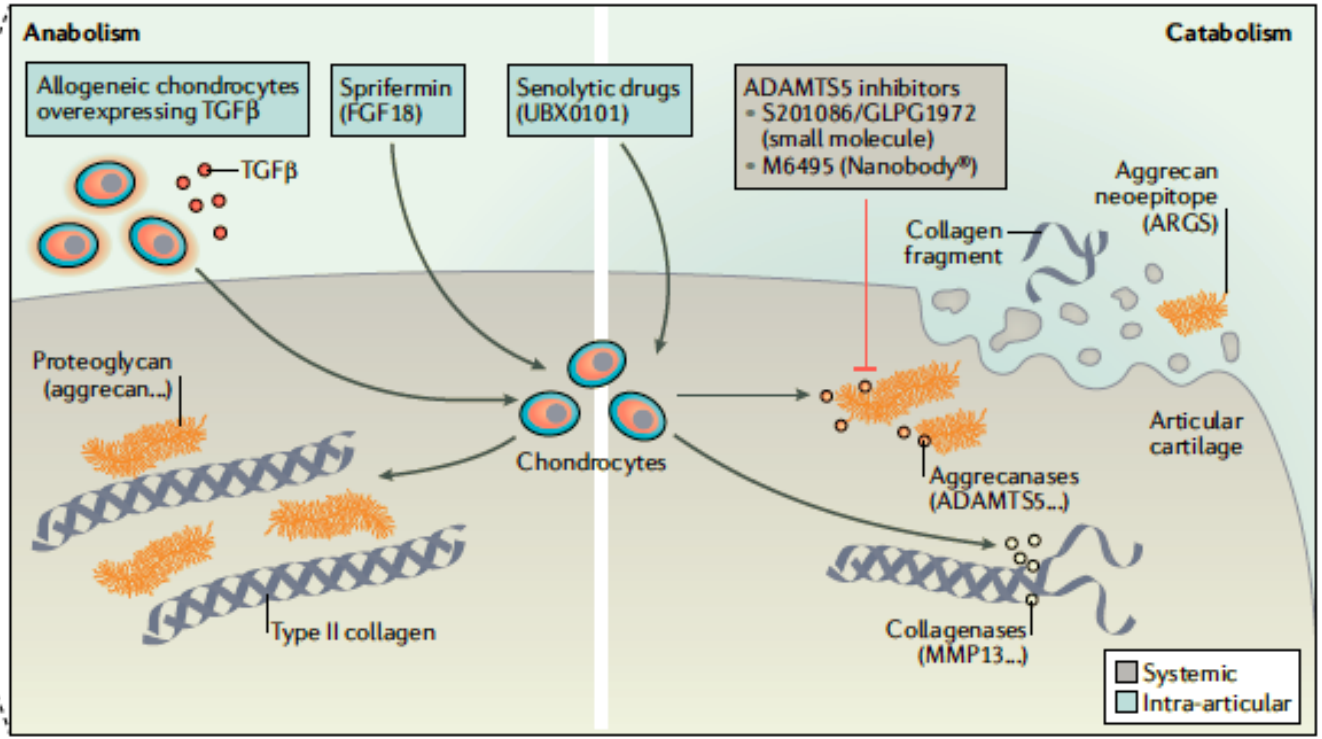


- STEROIDI
- ACIDO IALURONICO
- EMOCOMPONENTI A USO NON TRASFUSIONALE
- **NUOVI TRATTAMENTI**

Emerging pharmaceutical therapies for osteoarthritis

Augustin Latourte[1,2]✉, Margreet Kloppenburg[3,4] and Pascal Richette[1,2]





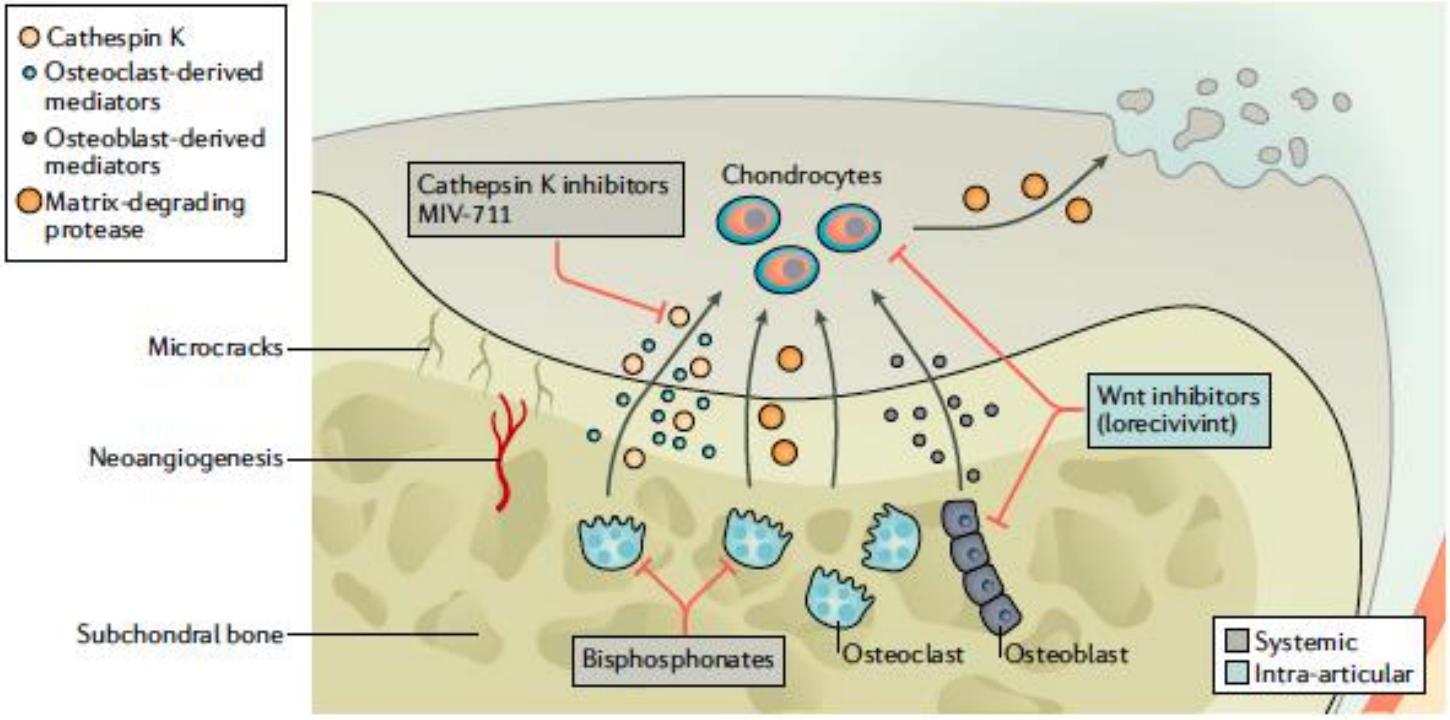
Drugs targeting cartilage breakdown or promoting cartilage repair in OA

One strategy is to **inhibit ECM-degrading enzymes** such as the protease ADAMTS5. **Inhibitors of ADAMTS5** in development include small-molecule inhibitors (such as GLPG1972/ S201086) and neutralizing antibodies (M6495), which are administered orally or subcutaneously, respectively; serum concentrations of aggrecan ARGS neoepitope, which is derived from the cleavage of aggrecan by ADAMTS5, can be used to monitor ADAMTS5 activity in vivo. Another strategy is to clear senescent chondrocytes, which produce pro- inflammatory mediators and ECM- degrading enzymes, from OA cartilage by use of **senolytic drugs** (for example, UBX0101). Finally, **ECM synthesis** by chondrocytes can be **enhanced using different growth factors**, such as **sprifermin** (rhFGF18, administered intraarticularly) or transforming growth factor- β (**TGFβ**; administered by intra- articular injection of allogeneic chondrocytes specifically designed to overexpress TGFβ).

Emerging pharmaceutical therapies for osteoarthritis

Augustin Latourte[1,2]✉, Margreet Kloppenburg[3,4] and Pascal Richette[1,2]

Drugs targeting subchondral bone remodelling in OA.

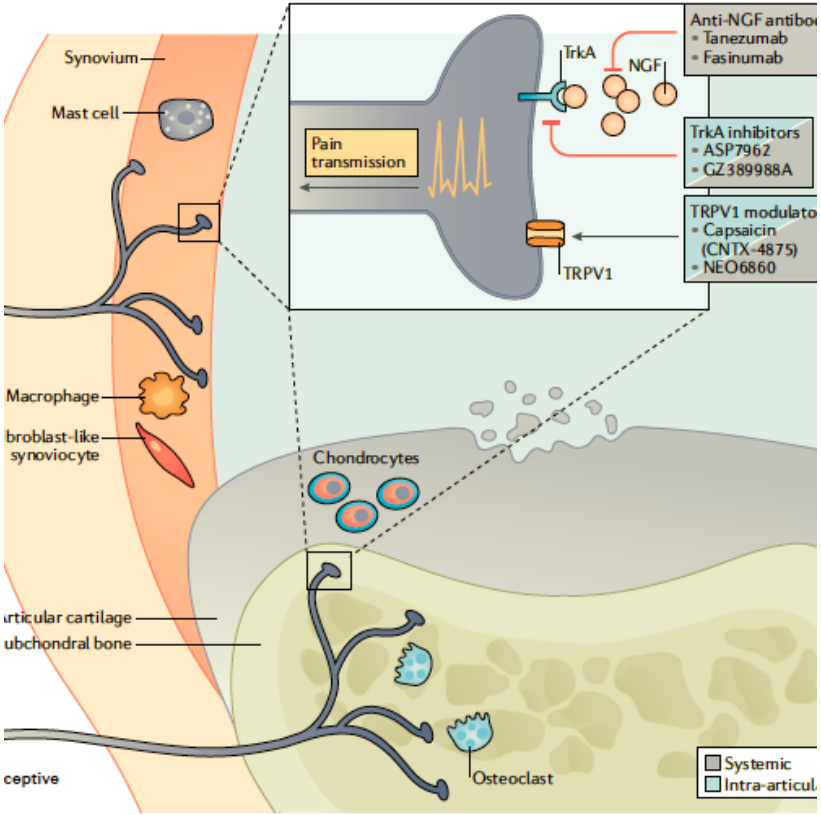


Cathepsin K, a protease produced mostly by osteoclasts as well as synovial cells, **is able to cleave type II collagen and represents an interesting therapeutic target in OA**. The orally administered cathepsin K inhibitor MIV-711 seems to limit cartilage damage and bone remodelling in knee OA. Another mechanism of joint damage in OA is hyperactivation of **Wnt signalling** in subchondral bone (especially in osteoblasts) and cartilage. **Lorecivivint, a Wnt inhibitor** administered by intra-articular injection, is a potential DMOAD under investigation for the treatment of knee OA.

Emerging pharmaceutical therapies for osteoarthritis
Augustin Latourte[1,2]✉, Margreet Kloppenburg[3,4] and Pascal Richette[1,2]

Drugs targeting pain in OA

Peripheral and central sensitization, the latter being characteristic of chronic pain, are important determinants of pain severity in OA. **Nerve growth factor (NGF), a neurotrophin** involved in peripheral sensitization, is an important regulator of OA pain and can be targeted by neutralizing antibodies **(tanezumab, fasinumab)**. These drugs, administered by subcutaneous injection**, can improve knee or hip OA pain and function but are associated with an increased risk of rapidly progressive OA.** The mechanisms underlying these joint- related adverse events are not fully elucidated. **Inhibitors of the NGF receptor tropomyosin-related kinase A (TrkA),** including ASP7962 (administered orally) or GZ389988A (administered intra-articularly), are also under investigation for the treatment of OA. **Transient receptor potential cation channel subfamily V member 1 (TRPV1),** an ion channel involved in the transmission of the pain stimuli through nociceptive neurons, **can be modulated by capsaicin**. Intra-articular injections of **CNTX-4875 (synthetic trans- capsaicin) could improve** knee OA- associated pain. Other TRPV1 modulators, such as NEO6860 (administered orally), are also being investigated in OA.



Safety, Tolerability, Pharmacokinetics, and Clinical Outcomes Following Single-Dose IA Administration of UBX0101, a Senolytic MDM2/p53 Interaction Inhibitor, in Patients with Knee OA

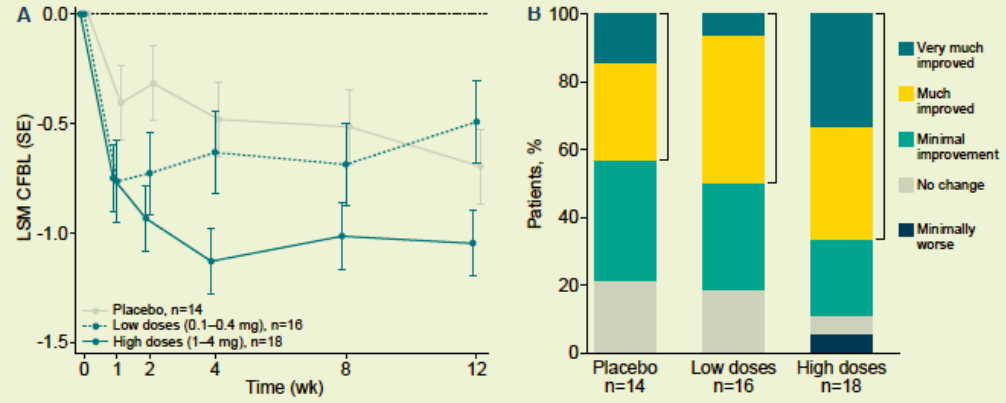
Benjamin Hsu[1], Jennifer Visich[1], Mark Genovese[2], Kimberly Walter[1], Mahru An[1], Remi-Martin Laberge[1], Jamie Dananberg[1]

[1]UNITY Biotechnology, Brisbane, CA; [2]Stanford University, Palo Alto, CA, USA

UNITY

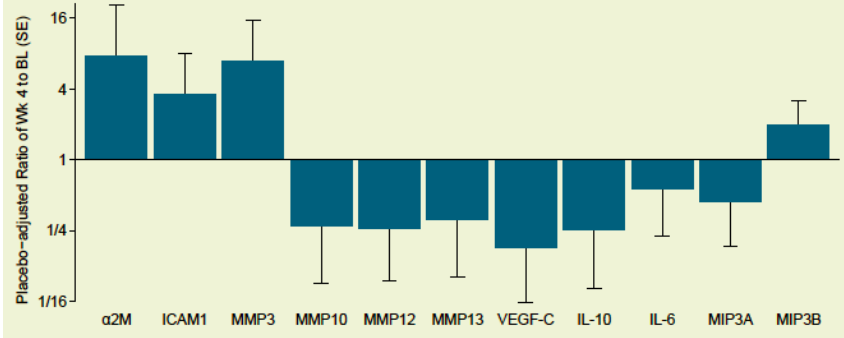
Senescent cell (SnC) is burden in OA synovial tissue to correlate with disease severity, inflammation, and knee pain UBX0101 is a mouse double minute 2 homolog (MDM2)/p53 interaction inhibitor that can induce apoptosis of SnCs; clearance of SnCs from joints by UBX0101 may create a pro-regenerative environment and lead to pain reduction.

Patients With OA Treated with UBX0101 Reported a Dose-Dependent Improvement of Function (A; WOMAC-C) and a Greater Impression of Change (B; PGIC) at Wk 12 vs Placebo



PGIC, patient global impression of change.

Biomarker Substudy: Modulation of SASP and OA-related Markers in Synovial Lavage 4 Wks Following a Single IA Administration of UBX0101 4 mg

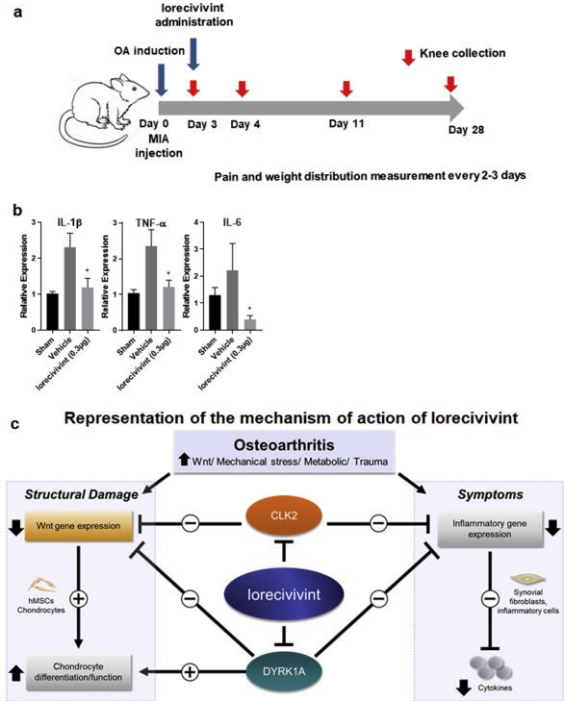


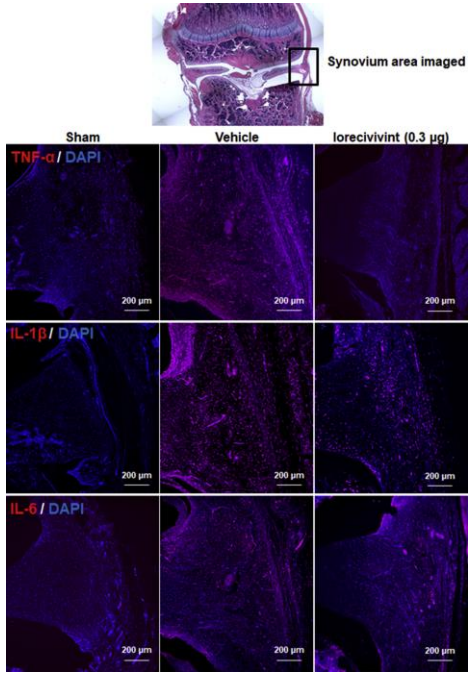
α2M, α2 macroglobulin; ICAM, intercellular adhesion molecule; IL, interleukin; MIP, macrophage inflammatory protein; MMP, matrix metalloproteinase; VEGF, vascular endothelial growth factor. Paired fluid analyses from UBX0101 group, n=14; placebo group, n=6.

- Synovial/lavage fluid analyses in the BMK substudy revealed modulation of multiple SASP/OA markers such as tissue remodeling and inflammatory factors, after UBX0101 IA compared to placebo

Wnt pathway upregulation contributes to **knee OA** through **osteoblast differentiation**, increased catabolic enzymes, and inflammation. The small-molecule Wnt pathway inhibitor, **lorecivivint**, was evaluated to elucidate its mechanism of action.

Lorecivivint is a small-molecule, intra-articular CLK/DYRK1A inhibitor which modulates the Wnt pathway and has demonstrated **beneficial effects on patient-reported outcomes** in two Phase 2 trials in subjects with knee OA relative to placebo.





Deshmukh V et al, Osteo Cart. 2019

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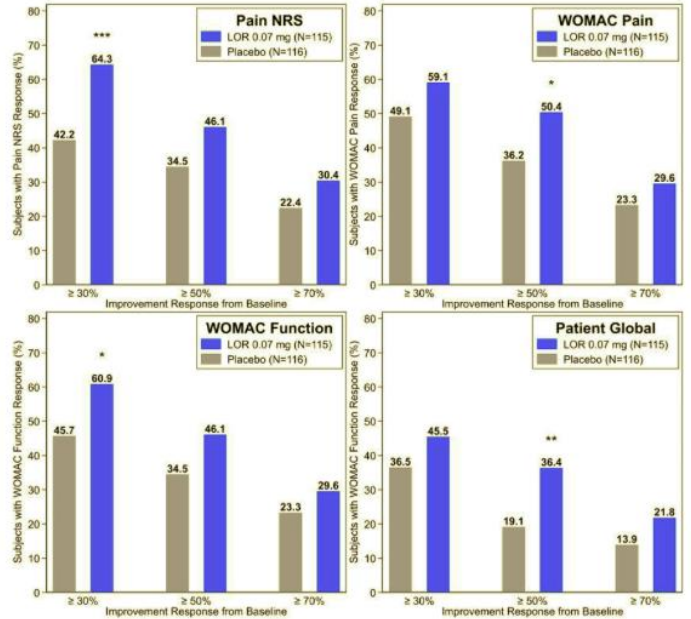
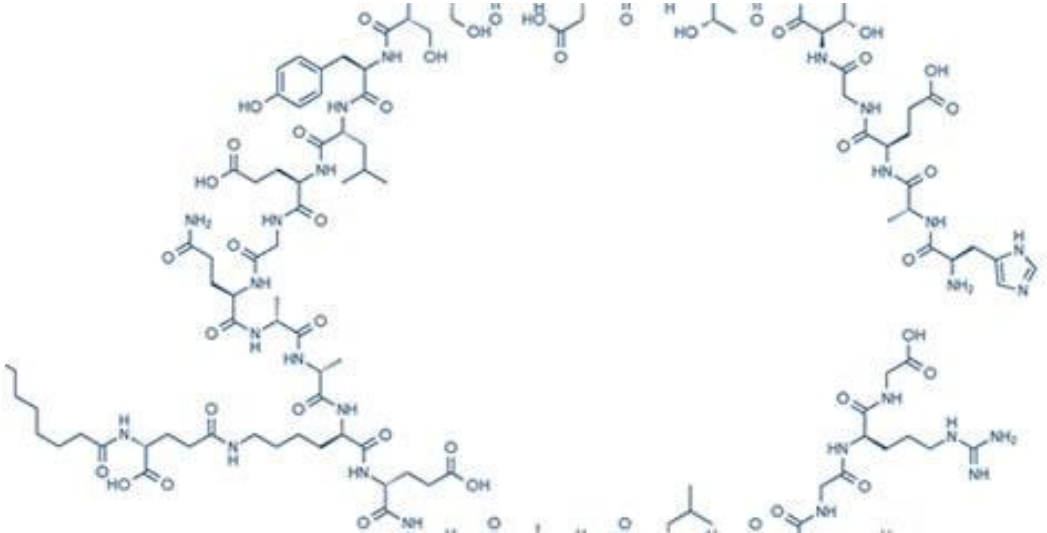
Yazici Y et al Poster 1327 ACR 2019



*P<0.05, **P<0.01,***P<0.001 from logistic regression vs. placebo using FAS All Subjects non-responder imputation.

LIRAGLUTIDE

• La liraglutide è un **principio incretino-mimetico** (analogo del peptide-1 simil-glucagone **GLP-1**, ormone endogeno incretinico che potenzia la secrezione di insulina glucosio-dipendente dalle cellule beta del pancreas) utilizzato nel trattamento del diabete mellito di tipo 2 e nel trattamento dell'obesità e del sovrappeso.



Que et al. Journal of Inflammation (2019) 16:13
https://doi.org/10.1186/s12950-019-0218-y

Journal of Inflammation

RESEARCH Open Access

The GLP-1 agonist, liraglutide, ameliorates inflammation through the activation of the PKA/CREB pathway in a rat model of knee osteoarthritis

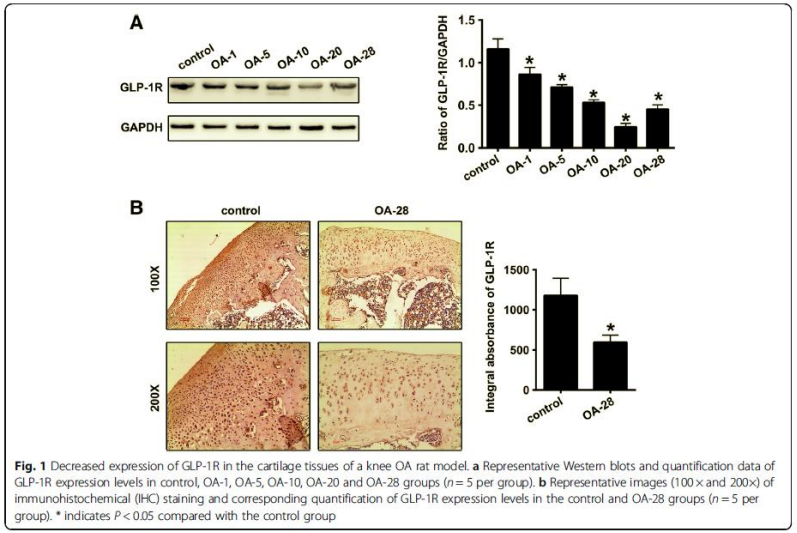


Fig. 1 Decreased expression of GLP-1R in the cartilage tissues of a knee OA rat model. **a** Representative Western blots and quantification data of GLP-1R expression levels in control, OA-1, OA-5, OA-10, OA-20 and OA-28 groups ($n = 5$ per group). **b** Representative images (100× and 200×) of immunohistochemical (IHC) staining and corresponding quantification of GLP-1R expression levels in the control and OA-28 groups ($n = 5$ per group). * indicates $P < 0.05$ compared with the control group

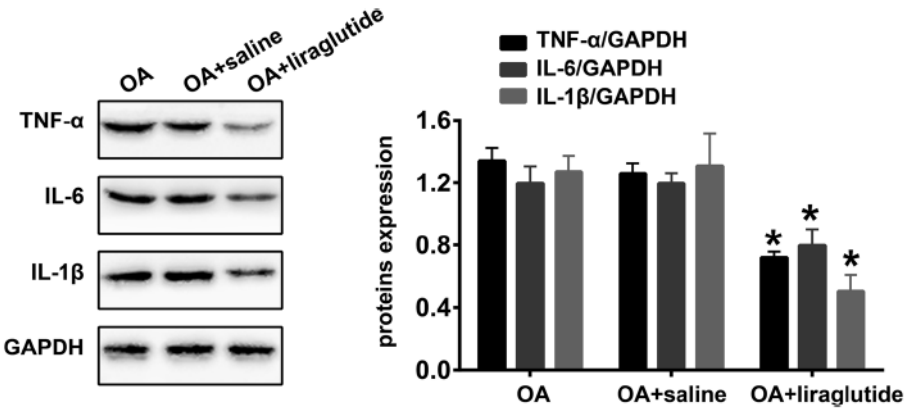


Fig. 6 Liraglutide ameliorates inflammation in the knee OA rat model. Representative Western blots and quantification data for TNF-α, IL-6 and IL-1β in the "OA", "OA + saline" and "OA + liraglutide" groups (n = 5 per group). * indicates $P < 0.05$ compared with the "OA + saline" group

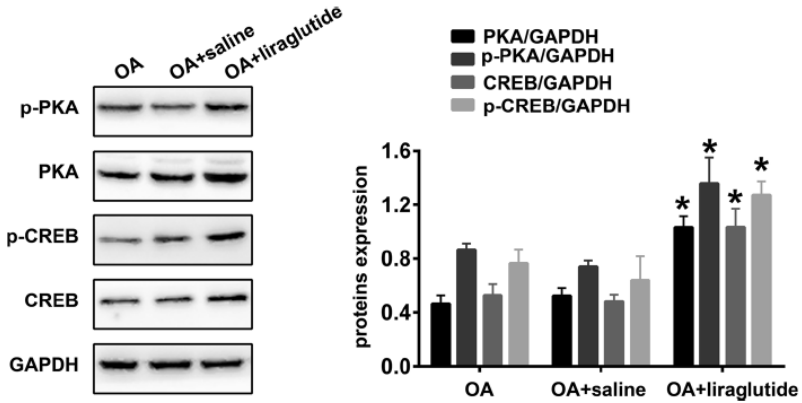


Fig. 5 Liraglutide activates the PKA/CREB pathway in cartilage tissues of the knee OA rat model. Representative Western blots and quantification data of PKA, p-PKA, CREB and p-CREB in the "OA", "OA + saline" and "OA + liraglutide" groups (n = 5 per group). * Indicates $P < 0.05$ compared with the "OA + saline" group

Chen et al. Cell Death and Disease (2018)9:212
DOI 10.1038/s41419-017-0217-y

Cell Death & Disease

ARTICLE Open Access

Glucagon-like peptide-1 receptor regulates endoplasmic reticulum stress-induced apoptosis and the associated inflammatory response in chondrocytes and the progression of osteoarthritis in rat

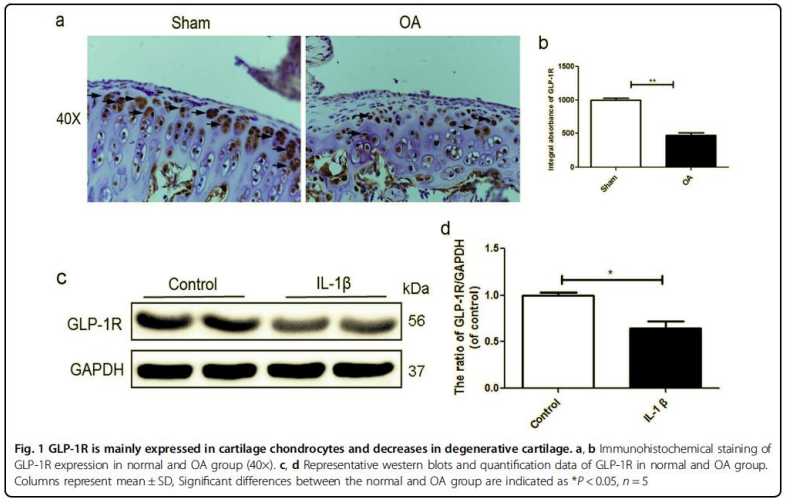


Fig. 1 GLP-1R is mainly expressed in cartilage chondrocytes and decreases in degenerative cartilage. a, **b** Immunohistochemical staining of GLP-1R expression in normal and OA group (40×). **c**, **d** Representative western blots and quantification data of GLP-1R in normal and OA group. Columns represent mean ± SD, Significant differences between the normal and OA group are indicated as $^{*}P < 0.05$, $n = 5$

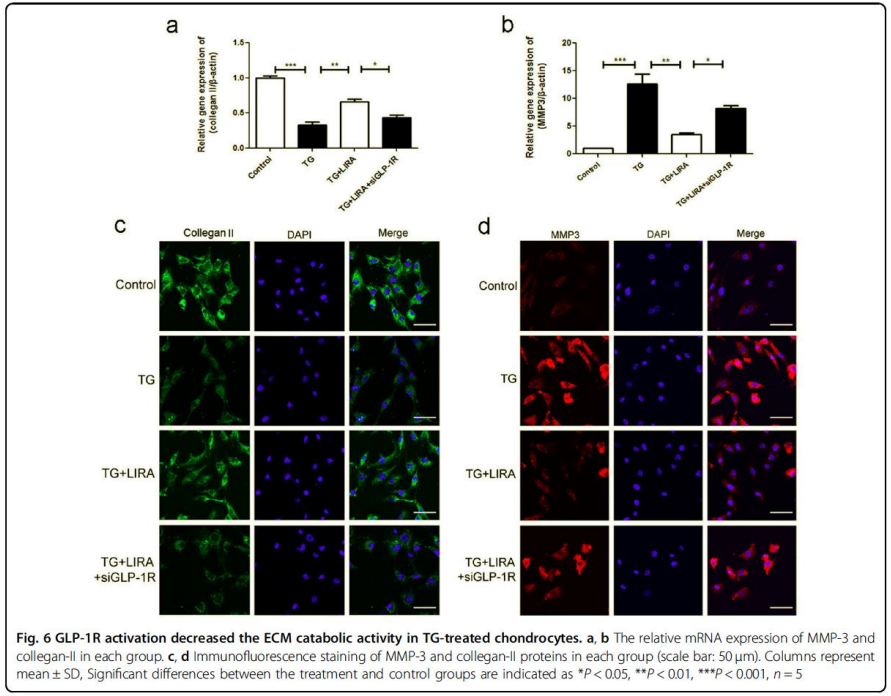


Fig. 6 GLP-1R activation decreased the ECM catabolic activity in TG-treated chondrocytes. a, **b** The relative mRNA expression of MMP-3 and collegan-II in each group. **c**, **d** Immunofluorescence staining of MMP-3 and collegan-II proteins in each group (scale bar: 50 μm). Columns represent mean ± SD, Significant differences between the treatment and control groups are indicated as $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $n = 5$

L'Infiammazione svolge un ruolo fondamentale nei processi metabolici della ECM e prove crescenti suggeriscono che **l'infiammazione** mediata dalla **sovraespressione** delle **MMP** si traduce in un **processo catabolico della matrice**

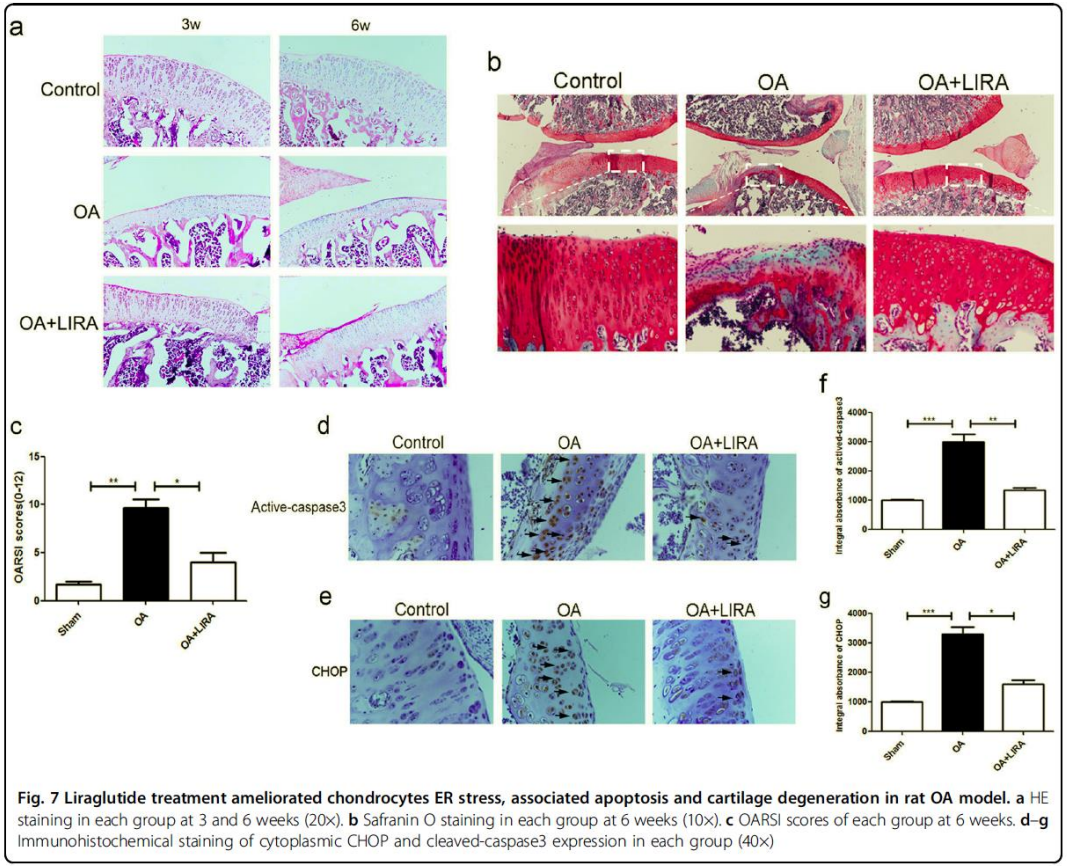


Fig. 7 Liraglutide treatment ameliorated chondrocytes ER stress, associated apoptosis and cartilage degeneration in rat OA model. a HE staining in each group at 3 and 6 weeks (20×). **b** Safranin O staining in each group at 6 weeks (10×). **c** OARSI scores of each group at 6 weeks. **d**–**g** Immunohistochemical staining of cytoplasmic CHOP and cleaved-caspase3 expression in each group (40×)

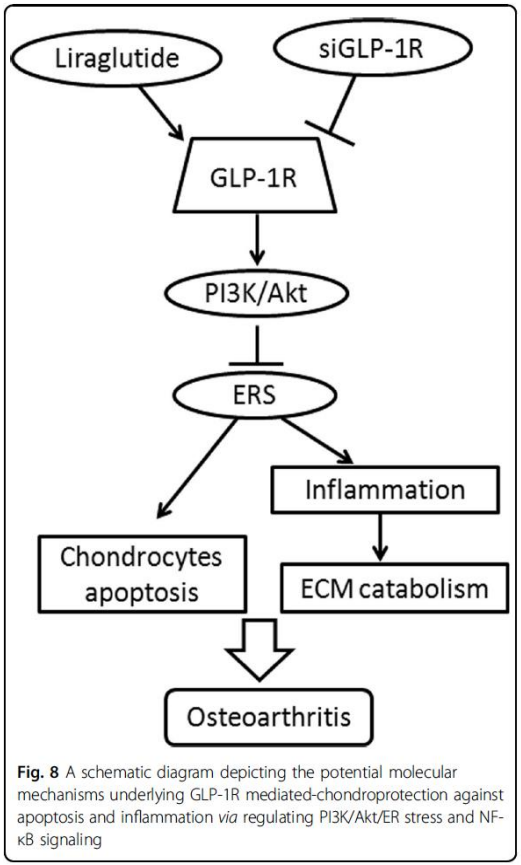
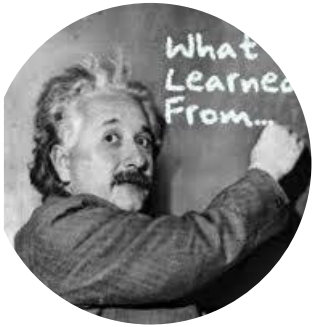


Fig. 8 A schematic diagram depicting the potential molecular mechanisms underlying GLP-1R mediated-chondroprotection against apoptosis and inflammation *via* regulating PI3K/Akt/ER stress and NF-κB signaling

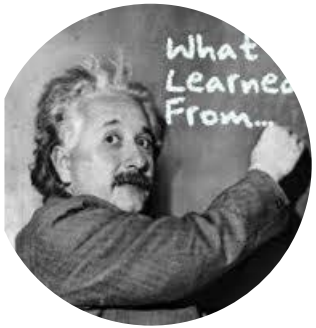
Gli effetti protettivi del GLP-1R potrebbero essere mediati dalla pathway **PI3K / Akt** che **inattiva** anche **pro-caspase-9** e provoca la defosforilazione di **caspase9**, **diminuendo** il livello di **apoptosi**.

L' Attivazione di **GLP-1R riduce** i livelli di **Bax pro-apoptotico** e di cleaved-caspase3, e **aumenta** i livelli di **Bcl-2 anti-apoptotico** nei condrociti trattati con IL-1β per OA, indicando che GLP-1R può essere un potenziale bersaglio per il trattamento dell'OA.



CONCLUSIONI

- La terapia intra-articolare costituisce un valido supporto per il trattamento dell'OA e dei RMSD
- L'US ottimizza la Tecnica Infiltrativa.
- La terapia infiltrativa con HA è una procedura relativamente sicura e con scarsi effetti collaterali sistemici, ma sono necessari studi rigorosi.
- L'efficacia della terapia con HA sembra correlare in modo proporzionale alla sua concentrazione e permette la riduzione dell'assunzione complessiva di FANS.



CONCLUSIONI

- La riduzione delle MMP e delle citochine pro-infiammatorie potrebbe in parte spiegare la particolare efficacia nei pazienti con coinvolgimento infiammatorio sinoviale.
- La terapia intra-articolare con EC potrebbe dimostrarsi un' ulteriore alternativa, a fronte di un migliore approccio metodologico della ricerca scientifica e un'opportuna standardizzazione.
- I nuovi trattamenti come Senolitici, Inibitori della via Wnt, agonista di GLP-1, rappresentano un nuovo approccio per il trattamento dell'OA e sembrano esercitare un prezioso effetto protettivo contro lo stress ossidativo, l'infiammazione e la degradazione della cartilagine.