HA VISCOSUPPLEMENTATION IN OA TREATMENT

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Vivalia
Votre santé, notre quotidien

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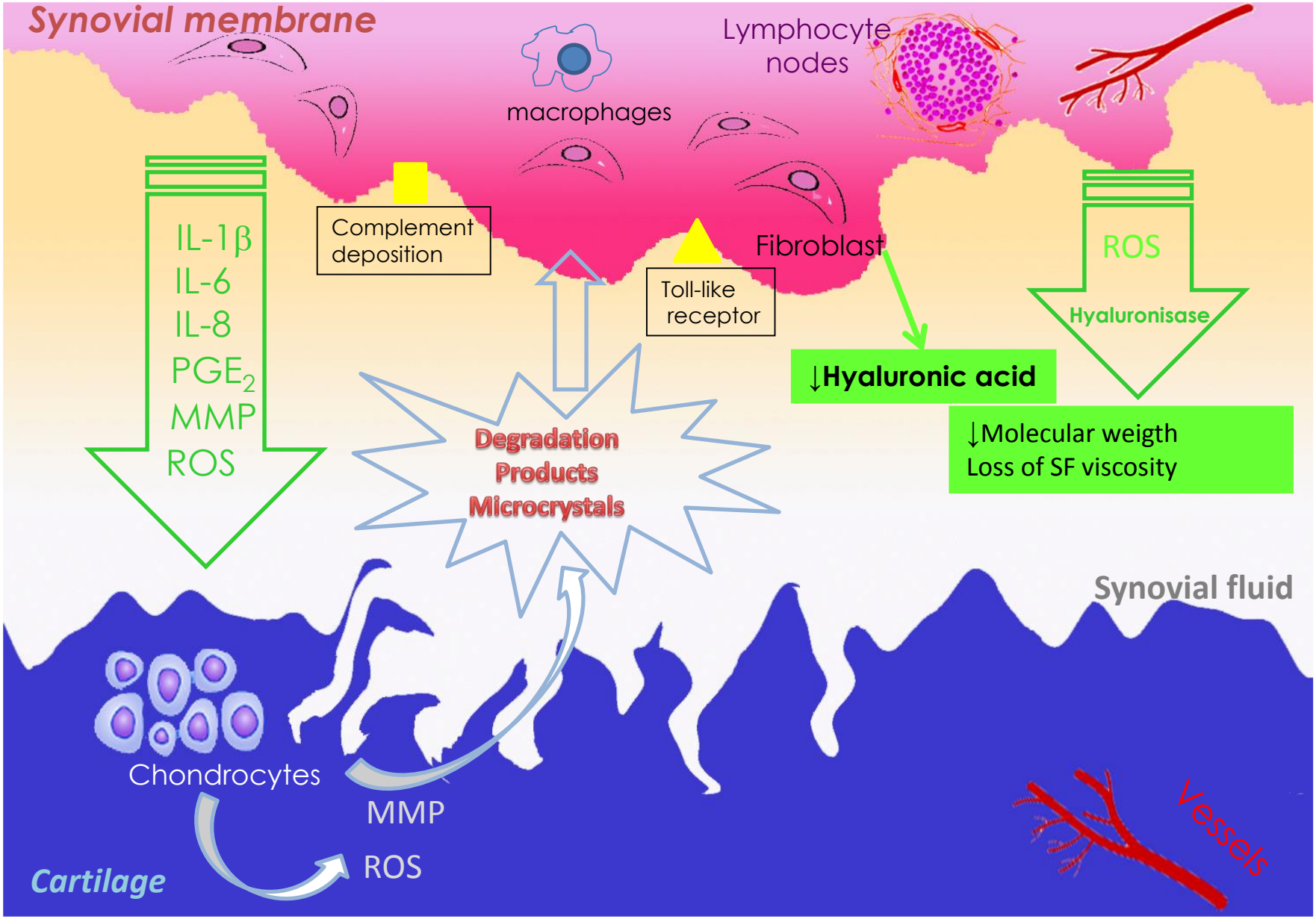
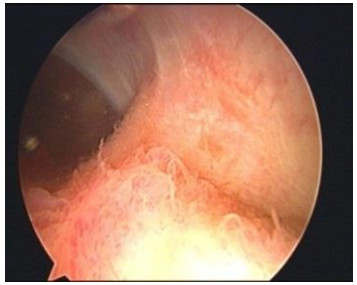
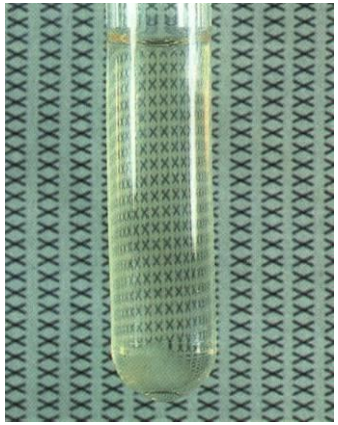
Bone and Cartilage Research Unit


Synovial membrane
Lymphocyte nodes
macrophages
Complement deposition
Toll-like receptor
Fibroblast
IL-1β
IL-6
IL-8
PGE2
MMP
ROS
ROS
Hyaluronisase
↓Hyaluronic acid
↓Molecular weigth
Loss of SF viscosity
Degradation Products Microcrystals
Synovial fluid
Chondrocytes
MMP
ROS
Cartilage
Vessels

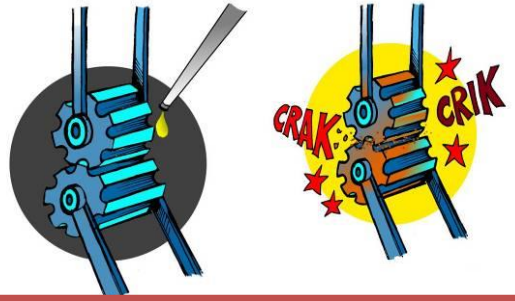
Loss of Synovial fluid lubrication properties





Synovial fluid: composition and properties	Healthy patient	Patient with osteoarthritis
Mw (MDa)	4 – 6	< 4
HA (mg/ml)	2,5 – 4	< 2
Elastic modulus (Pa à 2.5 Hz)	Close to 100	Close to 8
Viscous modulus (Pa à 2.5 Hz)	Close to 45	Close to 5
Viscosity at rest (Pa.s)	2 – 40 5 Pa.s à 37 °C	0.1 à 1

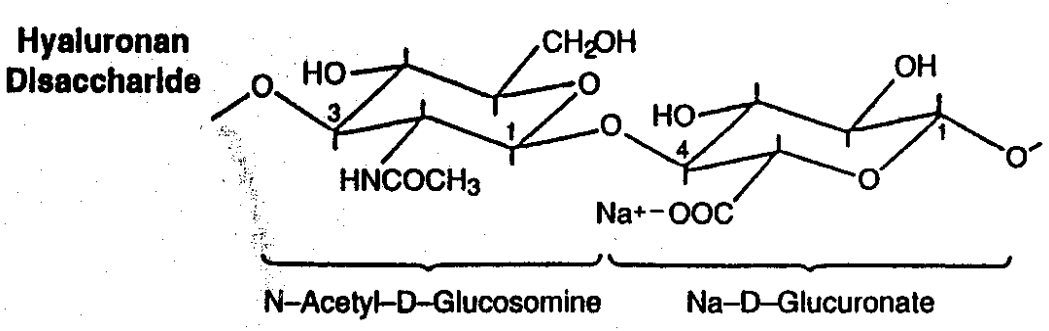
Pa: Pascal
Hz: Hertz
Pa.s: Pascal sec



Mansat C. Bulletin International du Mouvement 2007; 6: 3-4.

HYALURONIC ACID

- Synthesized by synoviocytes (B)
- Released into the synovial space
- HA belongs to the family of glycosaminoglycans
- HA is composed of 1000s of repeating disaccharide units (N-acetylglucosamine and glucuronic acid)
- A long polysaccharide chain of different length with a high molecular weight
- Accumulates on cartilage and ligament surfaces (boundary-layer lubrication)

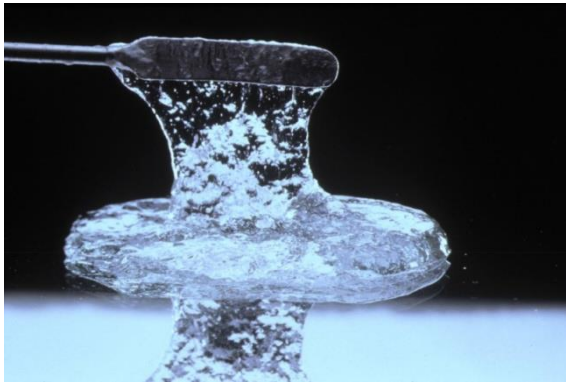


Viscosupplementation

"Viscosupplementation is the process that restores the normal rheological environment in the synovial fluid, synovial tissue…and reestablishes the protection, lubrication, shock absorption and barrier effects."

4 KEYS PROPERTIES
Visco-elasticity
Shock absorbing
Lubrication
Barrier effect

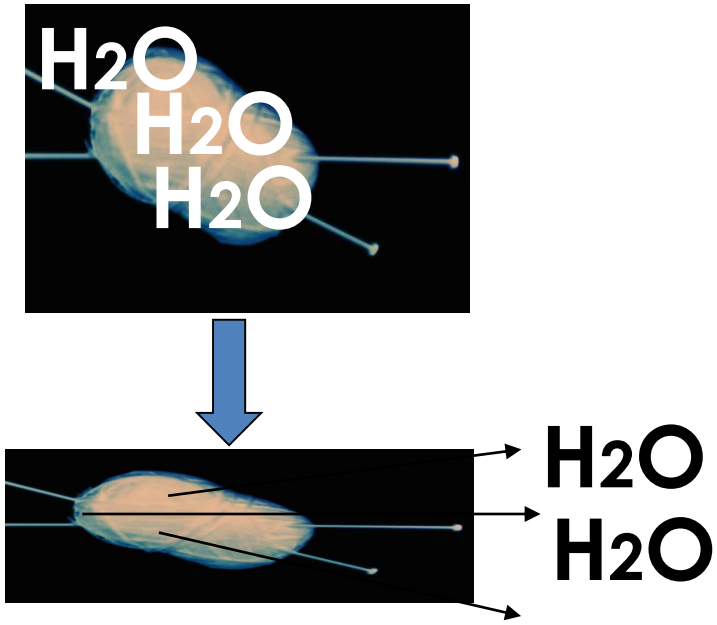
Hyaluronic acid



Balazs E.A. and Denlinger J.L. Journ. Rheumat. Suppl. 1993; 39: 3-9.

Mechanical effects

- Rheologic properties of the synovial fluid (visco-elastic)
- Shock absorbing (cushion)
- Lubrication



Gigante A. and Callegari L. Rheumat. Intern. 2010; 31 (4): 427-444.
Strauss E.J. et al. Am. Journ. Sports Med. 2009; 37 (8): 1636-1644.
Vitanzo P.C and Sennett B.J. Am. Journ. Orthopedics 2006; 421-428.
Altman R.D. et al. Osteoarthritis & Cartilage 2004: 12: 642-649.
Castellacci E. and Polieri T. Drugs Exptl. Clin. Res. 2004; XXX (29) : 67-73.

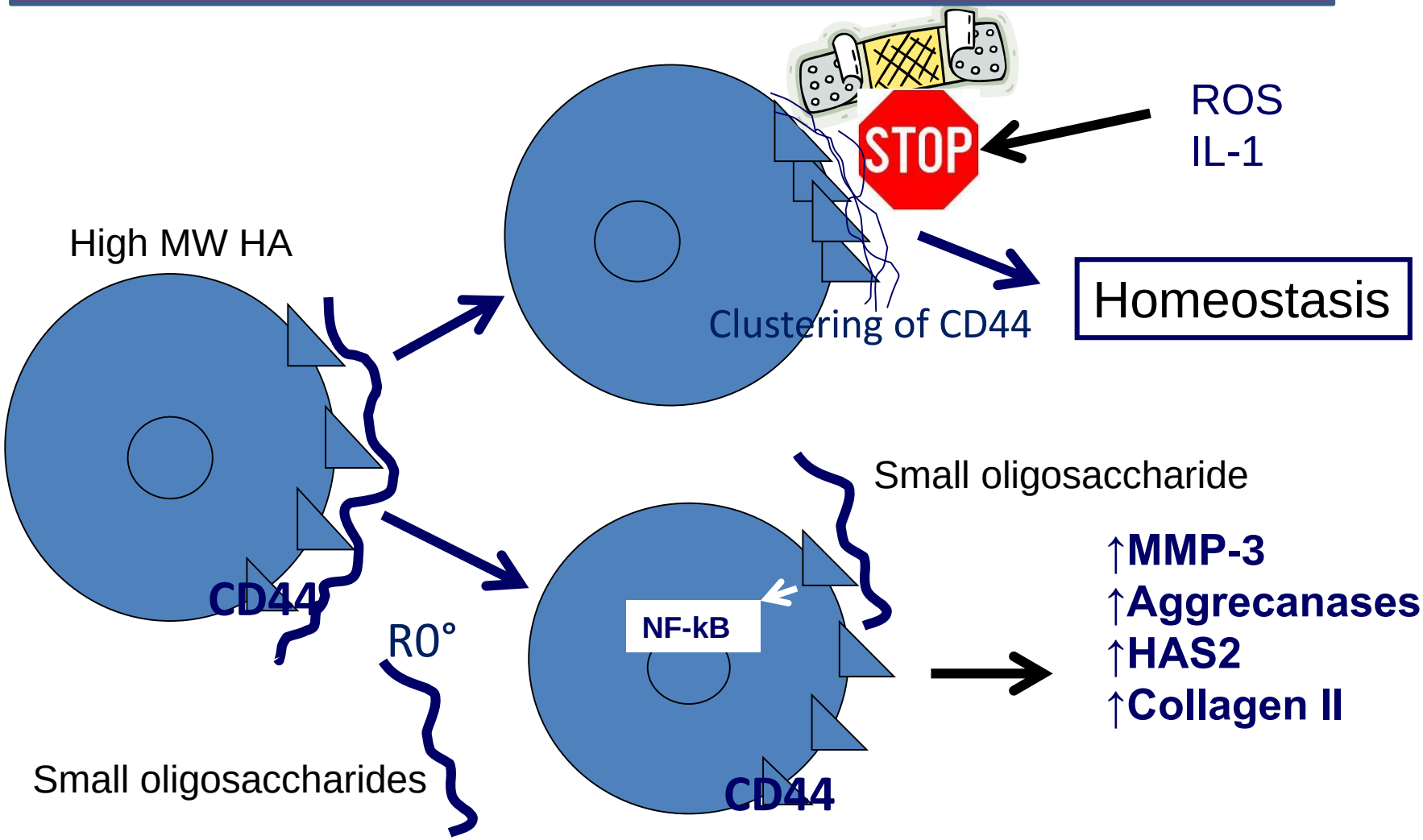
Viscoinduction

- The clinical benefits of intra-articular HA (e.g. restoration synovial cell metabolism, normalization HA biosynthesis) that go well beyond the physical lubricant/cushioning effect are defined as **VISCOINDUCTION**.

- Viscoinduction ensures that the effect is maintained for several months despite the short half-life of intra-articular HA

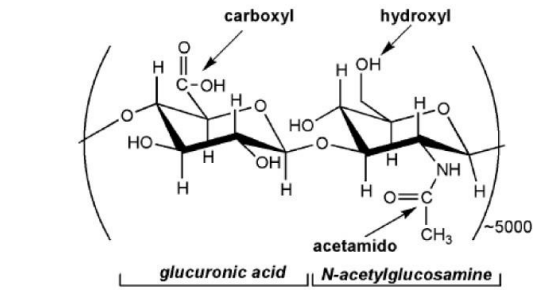
Gigante A. and Callegari L. Rheumat. Intern. 2010; 31 (4): 427-444.
Gosh P. and Guidolin D. Seminars Arthr. Rheum. 2002; 32 (1): 10-37.

Biological activities



Biological activity of HA

Cartilage
High MW HA
↑Proteoglycan production ↓NO induced chondrocyte apoptosis
Small HA oligosaccharides
↑Aggrecanases ↑MMP-3 ↑HAS-2 ↑Type II collagen



Toll-like receptors
CD44
RHAMM

Bone
?

Synovial membrane
High MW HA (>500kDa)
↑HA synthesis ↓Leukocytes migration and proliferation ↓Production of inflammatory and catbolic mediators
Small HA oligosaccharides
↑Angiogenesis

HA: different forms?

- Molecular weight: 0.7 to 92 Mda
- Concenration: 0.8 to 2%
- Prize : 0.83 to 4.13 € per mg.
- Chemical form: linear or cross-linked
- Origin : bacterial or animal
- Injection protocol: multiple or mono

HA in France in 2015

Trade name	Company	Vol/Conc. Ml/%	MW MDa	Nb of Injection	Price/ injection	Price/mg
Adant	Sankyo	2.5 (1)	0.9 – 1.2	5	100	1.33
Arthrum	LCA	2 (2)	2.4	3	100	0.83
Durolane	Genévrier	3 (2)	92	1	230	3.83
Euflexxa	Grunenthal	2 (1)	3	3	120	2
Go-On	Rottapharm	2.5 (1)	1.4	3	100	1.33
HappyCross	LABRHA	2 (1.6)	1.5	1	159	1.71
Hyalgan	Expanscience	2 (1)	0.5-0.7	3-5	88.32	1.47
Ostenil	TRB Chemica	2 (1)	1.2	3-5	100	1.66
Sinovial	Genévrier	2 (0.8)	0.8-1.2	3	100	2.08
Structovial Synocrom	Pierre Fabre Croma Pharma	2 (1)	1.6	3	100	1.66
Synvisc One	Sanofi	6 (0.8)	6	1	198.5	4.13

Mono-injection

Trade name	concentration
Synvisc One®	6 ml/48 mg
Durolane	3 ml/20 mg
Arthrum 2.5%®	3 ml/25 mg
Coxarthrum 2.5%®	3 ml/50 mg
Ostenil Plus®	2 ml/mannitol
Synocrom Forte One	4 ml/ 2%
Happy Cross®	2.2 ml/cross linked/mannitol

- ✓ Cross-linked
- ✓ Increased concentration
- ✓ Anti-oxidant (sorbitol or mannitol)

Antioxidant to protect HA

Trade name	Company	Form	Injection protocol	Indication	[HA&AO]	AO molecule
Happy Cross®	LABRHA	Cross-L	1/ 2.2 ml	Hip, ankle, shoulder	1.6 % 3.5 %	Mannitol
HappyMini®	LABRHA	Cross-L	1/ 1 ml	Thumb, TM, big toe	1.6 % 3.5 %	Mannitol
HappyVisc®	LABRHA	Linear	3/ 2 ml	Knee	1.55 % 3.5 %	Mannitol
Ostenil Plus®	TRB Chemedica	Linear	1-3/ 2ml	Knee, Hip, Ankle, shoulder	2 % 0.5 %	Mannitol
Synolis VA Go-On matrix®	APTISSEN	Linear	1-3/ 2ml	knee	2 % 4 %	Sorbitol

IAHA has a moderate effect on knee OA symptoms OARSI meta-analysis

(Zhang et al, 2010)

	ES Pain	ES Function
Acetominophen	0.14 (0.05,0.23)	0.09 (-0.03,0.22)
Diacerein	0.24 (0.08, 0.39)	0.14 (0.03, 0.26)
NSAIDs	0.29 (0.22,0.35)	-
Aerobic	0.52 (0.34; 0.70)	0.46 (0.25, 067)
Glucosamine Sulfate	0.58 (0,30, 0.87)	0.07 (-0.08,0,021)
IAHA	0.60 (0.37, 0,83)	0.61 (0.35,0.87)
Chondroitin sulfate	0.75 (0.50, 1.01)	-

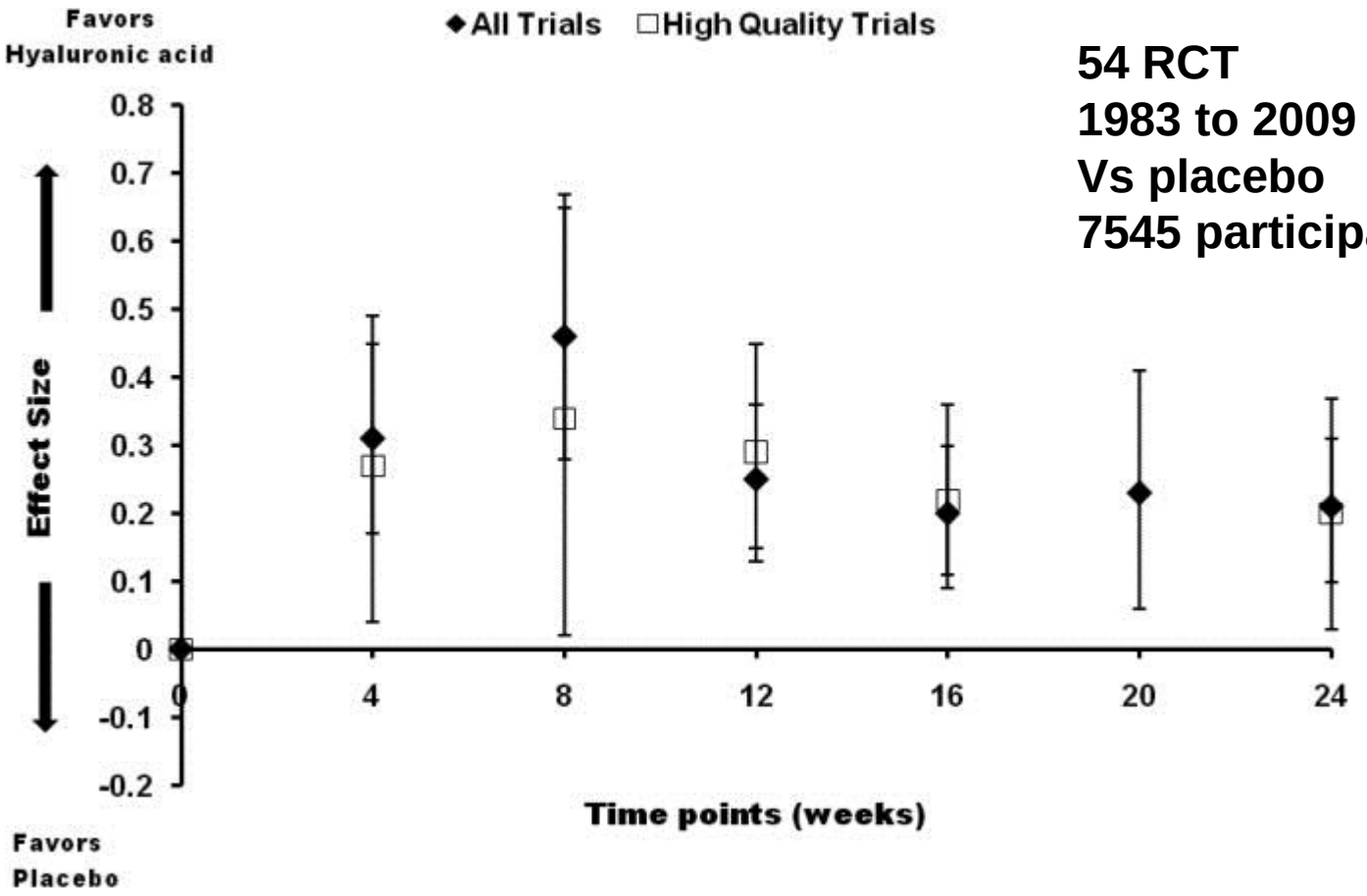
*All Studies

ES < 0.2 = None
ES 0.2 – 05 = Weak
ES 0.5 – 08 = Moderate
ES > 08 = Strong

versus placebo at 1-4 weeks

IAHA effect size is superior to NSAIDS with less GI adverse events
HA improves pain and function in knee OA

Bannuru meta-analysis knee OA



54 RCT
1983 to 2009
Vs placebo
7545 participants

Knee OARSI GUIDELINES

		ES Pain
2 weeks	In favour of IA Corticosteroids	0.39 (0.12-0.65)
4 weeks	=	0.01 (-0.21,0.23)
8 weeks	In favour of IAHA	0.22 (-0.5 ,0.49)
12 weeks	In favour of IAHA	0.35 (0.03, 0.66)

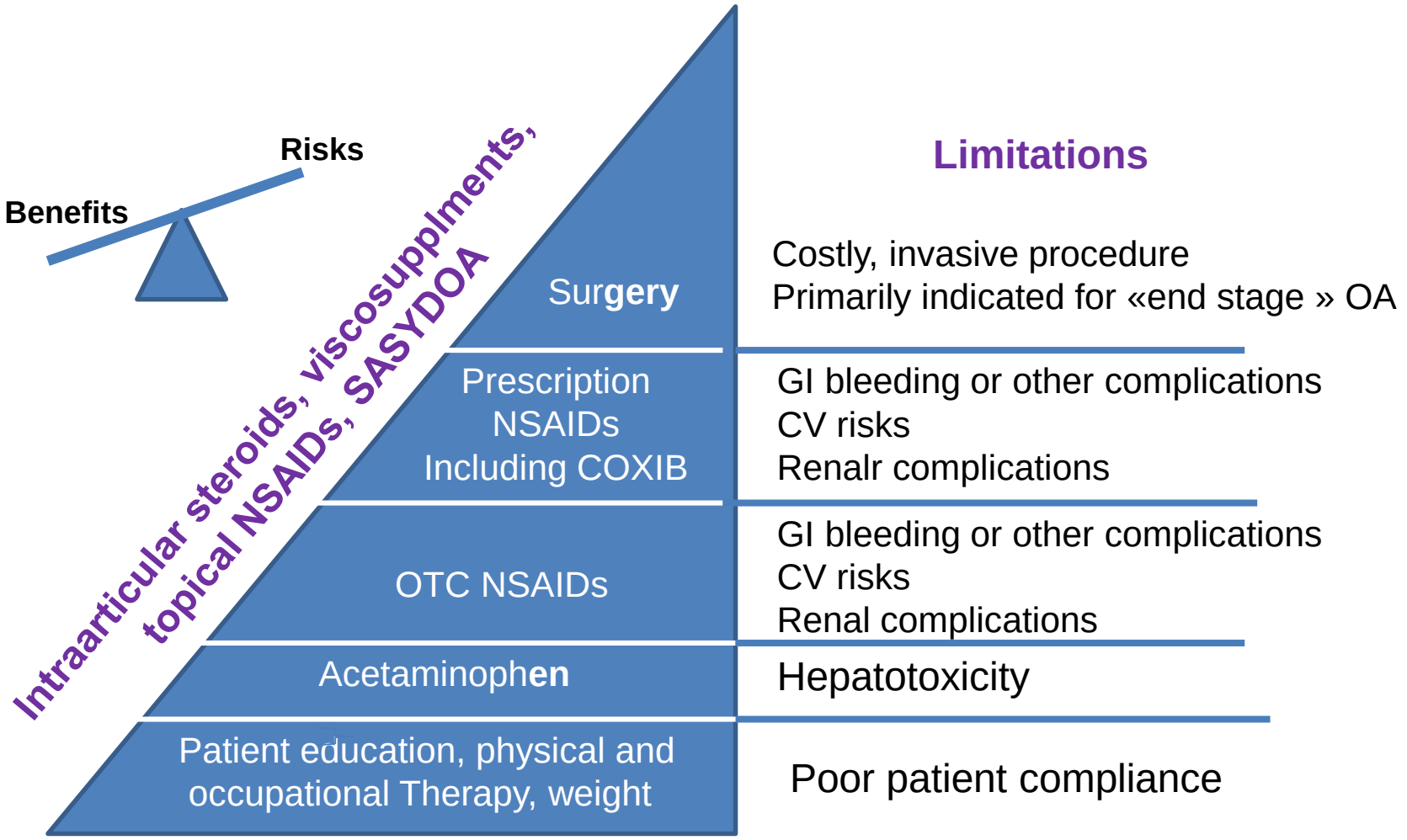
Comparing with intra-articular corticosteroids, benefits last generally longer!

Zhang W. et al. Osteoarthritis & Cartilage 2010; 18: 473-475.

Knee: HA in recent guidelines

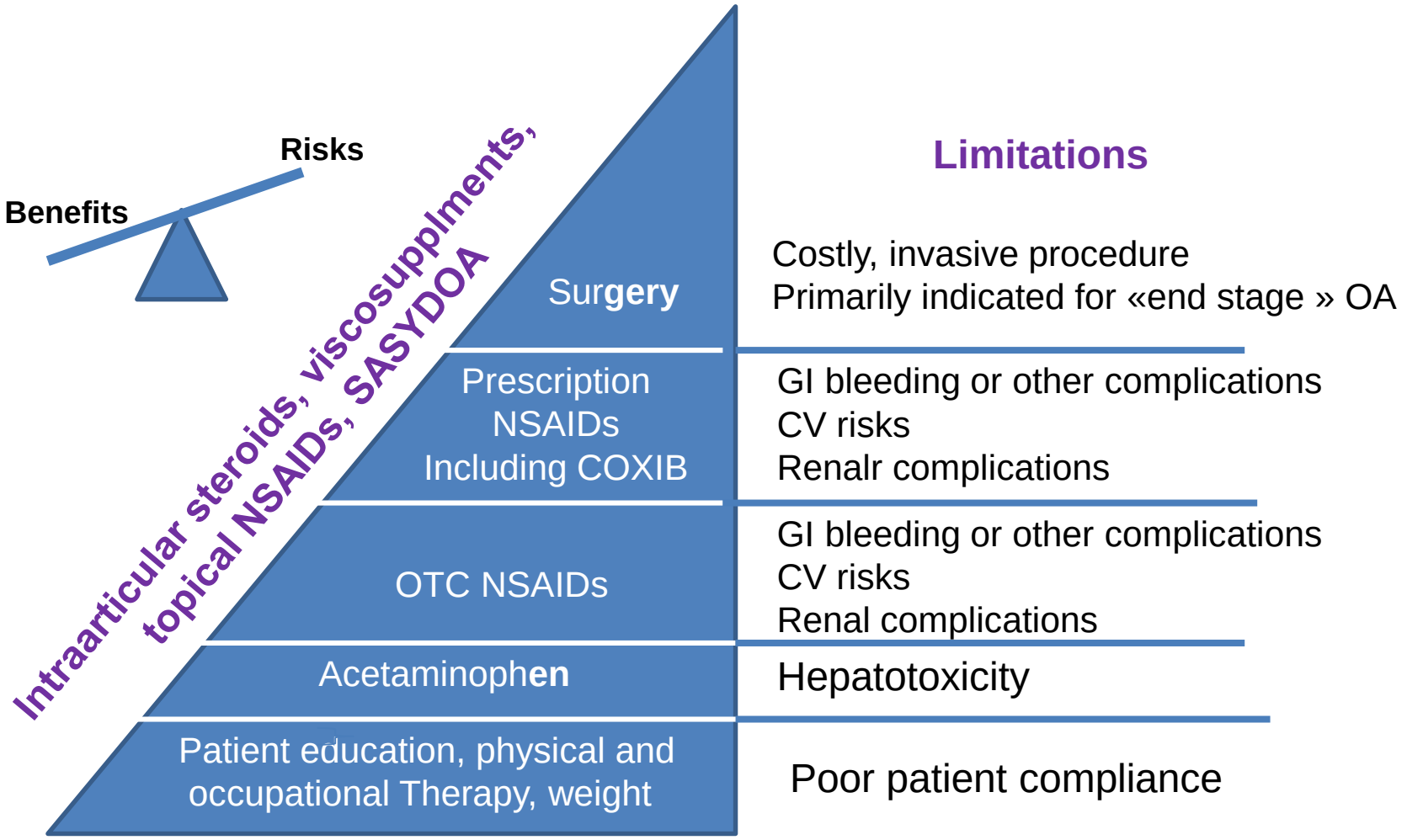
Society		Guidelines
ACR (2012)	American College of Rheumatology	« Conditionnally recommended to not use »
AAOS (2013)	American Association of Orthropaedic Surgeons	« Not recommended »
NICE (2014)	National Institute for Health and Clinical Excellence	« Do not offer intra-articular injection of hyaluronan for the management of OA »
OARSI (2014)	Osteoarthritis Research Society International	« Uncertain » let to the appreciation of the physician
« …iatrogenesis due to the overuse of NSAIDS, paracetamol and corticostéroids infiltration… » Letter of the « Section arthrose » of the French Society of Rheumatology to CNEDIMTS		

OA treatments and limitations



Modofied Clegg et al. Eur J Orthop Surg Traumatol, 2013

OA treatments and limitations



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Viscosupplementation

- **INDICATIONS**

→Treatment of symptoms associated with OA

- **CONTRAINDICATIONS**

→On-going joint inflammation (active synovitis)

→Crystals-induced arthropathy (gout, pseudogout)

→Infection

→ Anticoagulant treatments

→ Allergy to poultry

Viscosupplementation

- **Predictors of good outcome**

→Mild to moderate joint deformities

→Absence of large synovial effusion

→Well-preserved periarticular muscle mass

→Minimal joint instability

- **Predictors of good outcome**

→ BMI > 30

→K &L 4 No joint space

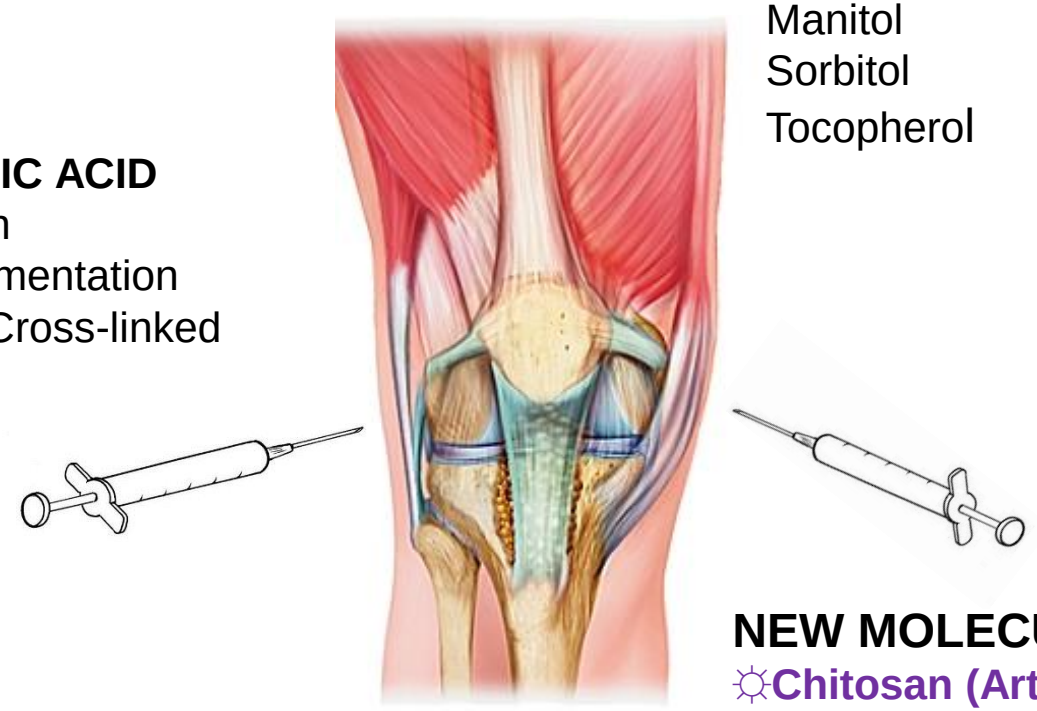
Conclusions

- IAHA is efficient and well tolerated
- The efficacy is moderate on pain and function
- Prolonged effect compared to corticosteroids
- The injection protocol should be assessed and respected
- Should be favor US guidance
- Indication and efficacy should be evaluated at individual levels (biomarkers – theranostic)

Viscosupplementation: new directions

Present

HYALURONIC ACID
Animal origin
Bacterial fermentation
Chemically Cross-linked



Future

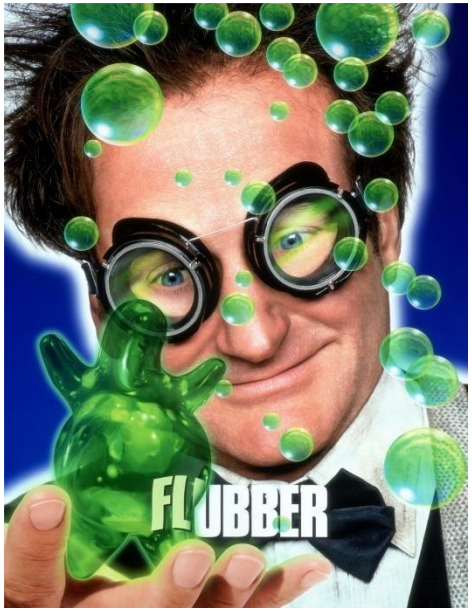
HA PROTECTION
Manitol
Sorbitol
Tocopherol

DRUGS/ANTIBODY DELIVERY
NSAIDS/Coxibs
Chlonidine
Triamcinolone
Doxycycline
☼**Chondroitin sulfate**
ADAMTS inhibitors

NEW MOLECULES
☼**Chitosan (Arthrovisc)**
Lubricine
Polynucleotides (Chondrotide)

Perspectives

So…What's about the future?



Viscosupplementation
Tribosupplementation
Drug delivery system
Biologic therapy

« Breakthough » product
Indication

Perhaps not only a dream!

Bone and Cartilage Research Unit

Team

MERCI!

International collaborations:

F Blanco (La coruna, Spain)
T Conrozier (CHU Lyon, France)
V Kraus (Duke University, USA)
L Punzi (University of Padova, Italy)
A Mobasheri (University of Notttingham, UK)
J Monfort (Hospital del mare (Spain)
P Richette (Lariboisiere, France)
J Runhaar (Erasmus MC, Rotterdam)