EFFECTS OF INTRA-ARTICULAR HYALURONIC ACID ASSOCIATED TO CHITLAC (ARTY-DUO®) IN A RAT KNEE OSTEOARTHRITIS MODEL

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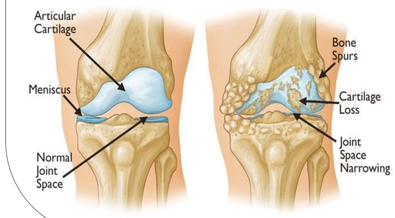
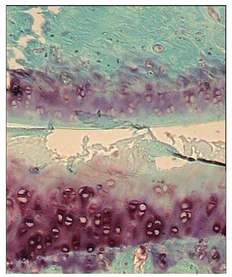
INTRODUCTION

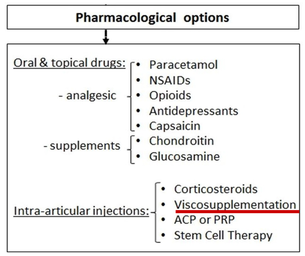
OSTEOARTHRITIS

Osteoarthritis (OA) is the most frequent musculoskeletal disease that affects about 240 million people globally. Worldwide estimates are around 10% of men and 18.0% of women aged over 60 years. It is a multifactorial disease and this aspect is highlighted by the feature sand symptoms present during this condition.





CURRENT PHARMACOLOGICAL TREATMENTS !?



Among conventional OA treatments, i.a viscosupplementation with **hyaluronic acid (HA)** is used to restore joint viscoelasticity. However, the rapid clearance and elimination of HA may limit its application.

OUR AIM?

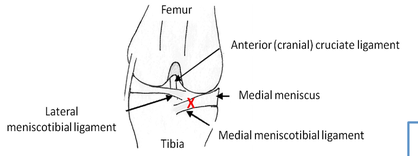
The aim of this study was **to verify the improved efficacy of HA within the joint, using a lactose-modified chitosan (chitlac) as a potentially chondroprotective additive** (ARTY-DUO®, Join-Therapeutics S.R.L., Como, Italy) on a OA animal model induced by destabilization of medial meniscus (DMM).

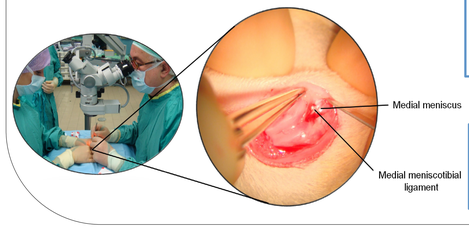
MATERIALS AND METHODS

EXPERIMENTAL DESIGN

Ethics Committee Approval: n° 0001860, 01/28/2016; Italian Ministry of Health Approval: n° 488/2016-PR, 05/17/2016

OA INDUCTION BY DESTABILIZATION OF MEDIAL MENISCUS





30 Rats → 4 weeks → OA

Once a week, for three weeks, i.a injections of:

(i) HA associated to chitlac (ARTY-DUO®) (n=10)
(ii) HA (n=10);
(iii) sodium chloride (NaCl) (n=10).

- Five animals for each group euthanized 4 weeks after the first i.a injection
- Five animals for each group euthanized 8 weeks after the first i.a injection

The restoration of physiological joint microenvironment was tested by:

- µ-CT (Ct.Th, mm; BV/TV, %; TbTh, mm; Tb.N, mm^{-1}; TbSp, mm; osteophytes volume, mm^3);
- Histology (OARSI and Mankin scores);
- Immunohistochemistry (MMP-3, MMP-13, Collagen II, Galectin I, Galectin II).

RESULTS

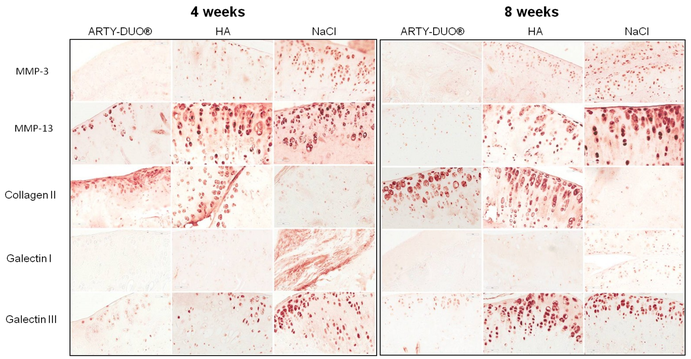
µ-CT

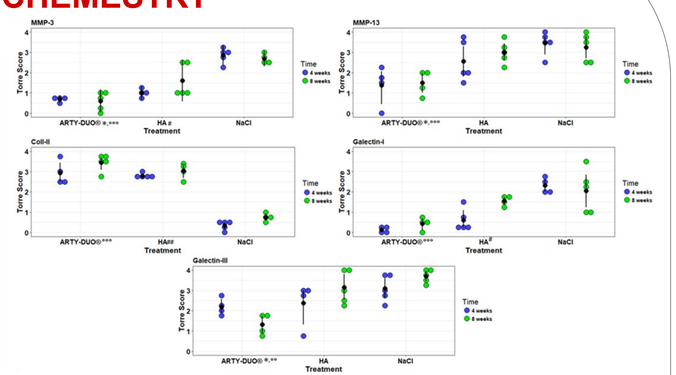
Trabecular and cortical parameters measured in distal femoral and proximal tibial epiphyses of treated knee joints with ARTY-DUO®, HA, or NaCl at 4 and 8 weeks after DMM surgery

	Distal femoral epiphysis			Proximal tibial epiphysis		
	ARTY-DUO®	HA	NaCl	ARTY-DUO®	HA	NaCl
BV/TV (%)						
4 weeks	36.12 ± 4.03 (32.92–39.33)	33.65 ± 1.21 (32.90–34.40)	34.00 ± 1.66 (32.97–35.03)	39.08 ± 3.55 (36.26–41.91)	35.48 ± 3.41 (33.36–37.59)	37.17 ± 3.13 (35.23–39.12)
8 weeks	37.86 ± 1.87 (36.64–38.97)	38.35 ± 2.63 (36.73–39.99)	36.25 ± 3.78 (33.91–38.60)	38.00 ± 2.67 (36.34–39.65)	38.78 ± 3.88 (36.37–41.19)	39.63 ± 4.12 (37.07–42.18)
Cs.Th (mm)						
Lateral						
4 weeks	0.231 ± 0.023 (0.20–0.24)	0.202 ± 0.017 (0.19–0.21)	0.205 ± 0.040 (0.18–0.23)	0.197 ± 0.016 (0.18–0.21)	0.183 ± 0.019 (0.17–0.19)	0.173 ± 0.015 (0.16–0.18)
8 weeks	0.221 ± 0.019 (0.21–0.23)	0.223 ± 0.034 (0.20–0.24)	0.237 ± 0.029 (0.22–0.25)	0.195 ± 0.020 (0.18–0.21)	0.202 ± 0.018 (0.24–0.26)	0.206 ± 0.027 (0.19–0.22)
Medial						
4 weeks	0.222 ± 0.021 (0.21–0.24)	0.218 ± 0.023 (0.20–0.23)	0.248 ± 0.013 (0.24–0.26)	0.180 ± 0.015 (0.17–0.19)	0.175 ± 0.025 (0.16–0.19)	0.190 ± 0.021 (0.18–0.20)
8 weeks	0.254 ± 0.041 (0.23–0.28)	0.251 ± 0.020 (0.19–0.21)	0.260 ± 0.028 (0.24–0.28)	0.193 ± 0.047 (0.16–0.22)	0.183 ± 0.026 (0.17–0.20)	0.193 ± 0.029 (0.17–0.21)xxx

	ARTY-DUO®	HA	NaCl
Osteophytes (mm^3)			
4 weeks	0.987 ± 0.039 (0.96–1.02)	0.962 ± 0.030 (0.94–0.98)	0.972 ± 0.039 (0.95–1.00)
8 weeks	0.998 ± 0.032 (0.98–1.02)	1.015 ± 0.027 (1.00–1.03)	1.004 ± 0.023 (0.99–1.02)

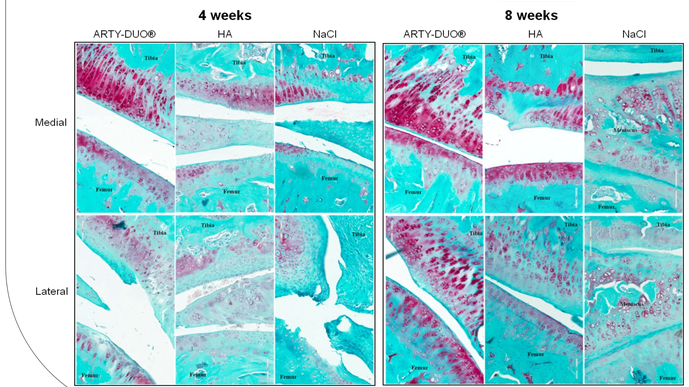
IMMUNOHISTOCHEMESTRY

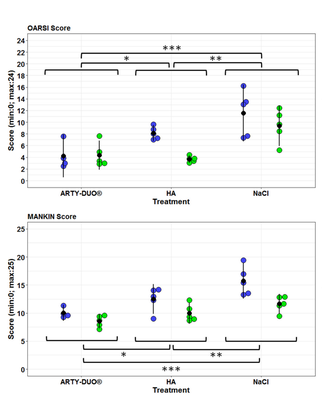




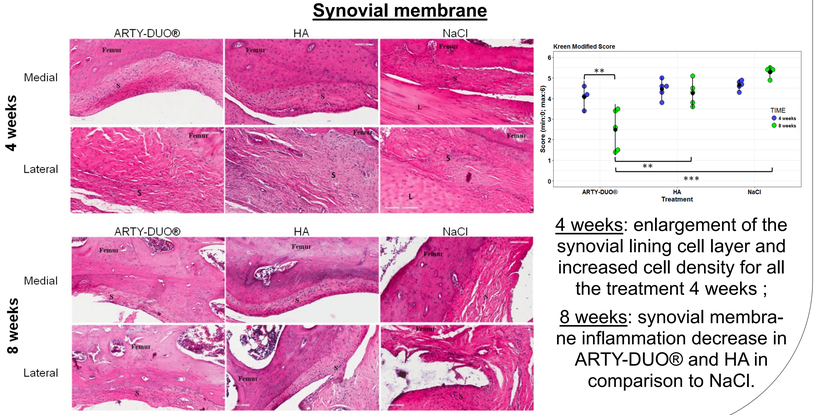
HISTOLOGY

Cartilage





Synovial membrane



4 weeks: enlargement of the synovial lining cell layer and increased cell density for all the treatment 4 weeks ;

8 weeks: synovial membrane inflammation decrease in ARTY-DUO® and HA in comparison to NaCl.

CONCLUSIONS

ARTY-DUO® enhanced articular cartilage structure and reduced catabolic enzymes, and therefore induced extracellular-matrix remodeling.

The reduction in MMPs was accompanied by the reduction in Galectins and by the increase of Collagen II which further underlines the synergistic actions of i.a. ARTY-DUO® injections in a rat knee OA model.

These preclinical data may contribute to improve the knowledge on the development of new disease modifying treatments.

COMPETING INTERESTS and ACKNOWLEDGEMENTS

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