Structural Effects of Intra-articular TGF-β1 Producing Cells in Moderate to Advanced Knee Osteoarthritis: MRI-Based Assessment in Randomized Controlled Trial with a Focus on Cartilage and Inflammatory Markers

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DISCLOSURES

- A Guermazi, FW Roemer and MD Crema are partners of Boston Imaging Core Lab (BICL), a company providing imaging assessment services
- A Guermazi is a Consultant to MerckSerono, TissueGene, OrthoTrophix, AstraZeneca, Pfizer, GE Healthcare and Sanofi-Aventis
- G Kalsi, O Copeland, M Noh are employees of TissueGene

BACKGROUND (1)

- TGF-β proteins
  - induce osteogenesis and chondrogenesis
  - play a role in cell growth, differentiation, and extracellular matrix protein synthesis
  - stimulate proteoglycan synthesis and chondrocyte proliferation
  - may also possess anti-inflammatory and immunosuppressive properties

BACKGROUND (2)

- One novel technique involves human chondrocytes transduced with a viral vector containing the gene for TGF-β1 transcription (TG-C)
- TG-C may have positive effects on pain levels (VAS and IKDC scores at 1 year) in patients who have moderate to advanced knee osteoarthritis [1]
- Patients receiving TG-C had more positive responses on the knee evaluation and pain, and they were less likely to require analgesic compared to placebo

[1] Cherian JJ, et al. Osteoarthritis Cartilage 2015;23:2109-18.

PURPOSE

- To assess effects of intraarticular TG-C on semi-quantitatively assessed MRI (sqMRI) features of knee OA compared with placebo treatment with a focus on safety and efficacy within a 12 months period

METHODS - STUDY SAMPLE

- A multi-center double-blind placebo-controlled randomized study (ClinicalTrials.gov identifier: NCT01221441)
  - IRB approval and patient consent obtained

- We included both male and female subjects
  - aged between 18 and 70 years
  - body mass index (BMI) between 18.5 and 45.5 kg/m^2
  - KL grade 3 radiographic knee osteoarthritis
  - pain symptoms for more than four consecutive months and intensity of ≥ 40 and ≤ 90 on the 100-mm scale

METHODS - Treatment

- Patients randomized to receive intraarticularly a 3:1 mixture of non-transduced allogeneic human chondrocytes and allogeneic human chondrocytes virally transduced to express TGF-β1 (TG-C) (TissueGene-C; TissueGene Inc., Rockville, Maryland, USA), or placebo (2 ml normal saline 0.9%)
- Patient's knee joints were aspirated to remove synovial fluid prior to GEC-TGF-β1 or placebo administration
- Treatment or placebo was injected via 18 gauge needle. Both patient and physicians were blinded at the time of injection

METHODS - MRI ASSESSMENT (1)

- 3T MRI at baseline and follow-up visits (3, 6, 12 months) performed in 4 US sites
- Triplanar intermediate-weighted fat suppressed sequences
- MRIs were assessed by one reader (18 years of experience in SQ MRI assessment of OA) in sequential order - unblinded to the time sequence of MRI but blinded to all clinical information including treatment

METHODS - MRI ASSESSMENT (2)

- MRIs were assessed using the WORMS system
  - cartilage morphology (grade 0-6)
  - bone marrow lesions (BMLs – grade 0-3)
  - meniscal damage (grade 0-4)
  - meniscal extrusion (grade 0-2)
  - Hoffa-synovitis (grade 0-2)
  - effusion-synovitis (grade 0-2)
  - Osteophytes (grade 0-7)

METHODS - MRI ASSESSMENT (3)

- Analyses included multi-dimensional assessment:
- (a) A delta-subregional approach was applied, which adds the *number of subregions* (total of 14 articular subregions for cartilage and BMLs on a knee level, 5 subregions each for the medial and lateral tibio-femoral [MTFJ, LTFJ] and 4 subregions for the patello-femoral [PFJ] compartment) showing worsening (>0), no change (0) or improvement (<0)
- (b) A delta-sum approach was used, which adds the absolute *scores of all subregions* combined per compartment or for the whole knee. Progression was defined as delta >0 for each assessment, separately
- (c) A third definition of progression was having worsening in any of the subregions
- Analyses were performed on a whole knee level and separately for MTFJ, LTFJ and PFJ compartments for all subgroups

METHODS - Statistical analysis

- Binary logistic regression with GEE was used to compare risks of progression, with adjustment for baseline age and gender
- Mann–Whitney–Wilcoxon tests assessed differences of the continuous assessments between treatment groups

RESULTS (1):

- Treatment group - 57 Patients
- Placebo group - 29 patients

- TG-C and placebo subgroup were comparable without statistically significant differences in regard to:
  - age (55.9 ± 7.9 vs. 56.6 ± 9.4 years)
  - gender (37 (64.9 %) vs 17 (58.6 %) female)

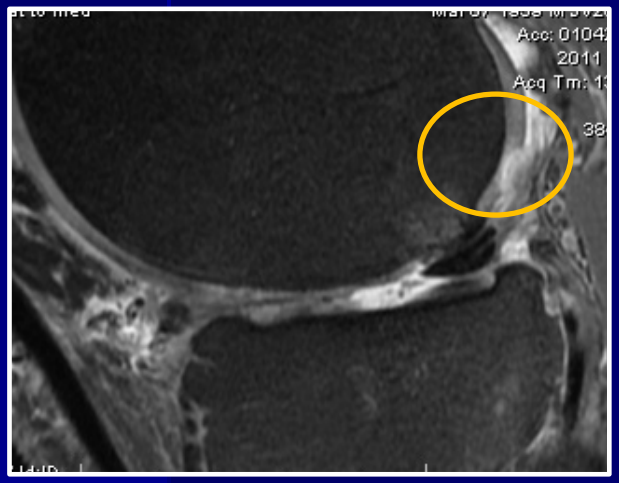
RESULTS (2):

Dichotomous cartilage morphology change treatment vs. placebo for all visits combined

		N of follow-up visits		N (%) of MRI progression		Analysis adjusted for age and gender	
Compartment	***Definition***	***T***	***P***	***T***	***P***	***RR (95% CI)***	***p-value***
Knee	Progression in any subregion	133	71	46 (34.6%)	34 (47.9%)	0.7 (0.5,1.0)	0.077
	Delta Subregion>0	123	71	43 (35.0%)	32 (45.1%)	0.8 (0.5,1.2)	0.207
	Delta Sum>0	123	71	26 (21.1%)	23 (32.4%)	0.6 (0.3,1.2)	0.176
Lateral TFJ	Progression in any subregion	133	71	20 (15.0%)	12 (16.9%)	0.8 (0.3,1.9)	0.617
	Delta Subregion>0	128	71	20 (15.6%)	12 (16.9%)	0.8 (0.4,1.9)	0.680
	Delta Sum>0	128	71	13 (10.2%)	10 (14.1%)	0.7 (0.2,1.9)	0.434
Medial TFJ	Progression in any subregion	133	71	23 (17.3%)	12 (16.9%)	1.1 (0.5,2.5)	0.767
	Delta Subregion>0	133	71	23 (17.3%)	12 (16.9%)	1.1(0.5,2.5)	0.767
	Delta Sum>0	133	71	16 (12.0%)	5 (7.0%)	1.9(0.5,7.2)	0.345
PF	Progression in any subregion	131	71	18(13.7%)	16(22.5%)	0.6(0.3,1.3)	0.176
	Delta Subregion>0	128	71	17(13.3%)	15(21.1%)	0.6(0.3,1.3)	0.210
	Delta Sum>0	128	71	10(7.8%)	10(14.1%)	0.5(0.2,1.9)	0.327

T = treatment group; P = placebo group; TFJ = tibiofemoral joint; RR = relative risk

RESULTS (2):



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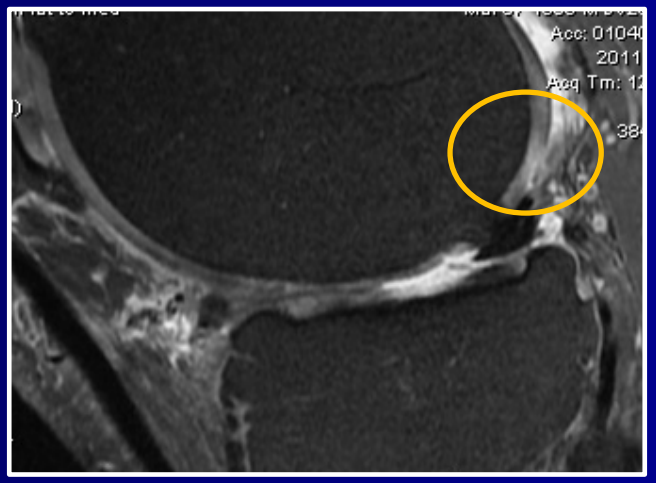

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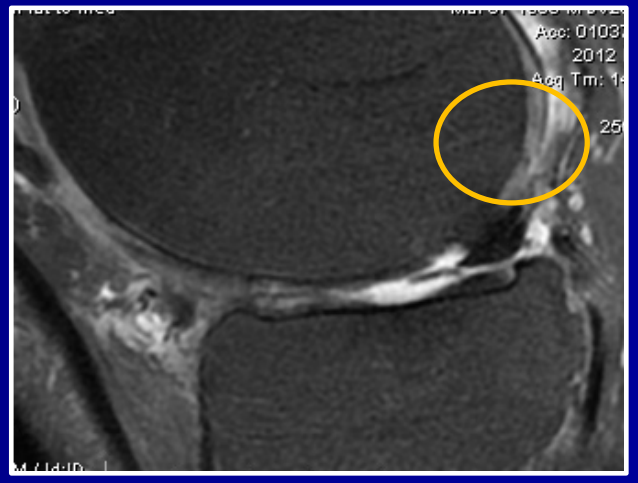

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RESULTS (3):

- **Dichotomous change of Hoffa-synovitis and effusion-synovitis in a whole knee for all visits combined**

		N of follow-up visits		N (%) of MRI progression		Analysis adjusted for age and gender	
MRI feature	***Definition***	***T***	***P***	***T***	***P***	***RR (95% CI)***	***p-value***
Hoffa-synovitis/ Effusion-synovitis combined	Any worsening	136	71	13 (9.6%)	15 (21.1%)	0.5 (0.2,1.2)	0.115
Hoffa-synovitis	Any worsening	133	71	4 (3.0%)	5 (7.0%)	0.3 (0.1,1.8)	0.200
Effusion-synovitis	Any worsening	136	71	12 (8.8%)	11 (15.5%)	0.6 (0.2,2.0)	0.428

T = treatment group; P = placebo group; RR = relative risk

RESULTS (4):

- No statistically significant difference between treatment and placebo groups in:
  - Osteophyte sum scores at week 52 visit
  - Change in BMLs and meniscal damage from baseline to 12 months
    - any worsening BMLs: 66.2% vs. 60.6%, p=0.612
    - any worsening meniscal damage: 31.6% vs. 32.4%, p=0.993

Discussion (1)

- Phase II trial of allogeneic human chondrocytes expressing TGF-β1 vs. placebo in patients with moderate to advanced OA

- No safety signal was observed for the treatment group in regard to potential hypertrophic osteophyte formation

Discussion (2)

- Less progression of cartilage damage and MRI markers of inflammatory changes were observed on a knee level for the treatment group
- Lack of statistical significance may partly be influenced by low rates of progression overall and limited number of patients

Conclusion

- Intraarticular TG-C seems to have potential to delay progression of cartilage damage and local inflammation, determined by semiquantitative MRI, in the knee joint with osteoarthritis
- A future study with a larger number and a longer follow-up period is necessary to observe effects with statistically significant results