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A Mechanistic and Clinical study of intra-articular Arthrosamid for knee osteoarthritis

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Faculty Disclosure Information

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- Professor Snow is a paid consultant for Contura

Introduction

- Osteoarthritis(OA) is a major contributor to morbidity worldwide.
- Arthrosamid® is a non-absorbable, biocompatible, injectable, transparent hydrogel comprising of 97.5% water and 2.5% of cross-linked polyacrylamide.
- It is indicated for the treatment of osteoarthritis of the knee and has demonstrated clinical benefit compared to Hyaluronic acid.
- The aim of this study was to confirm the clinical effectiveness of Arthrosamid for Knee OA and to investigate its potential mechanism of action.

Primary and secondary outcome measures

- The primary outcome measure was the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score at 6 months post injection. Secondary outcomes measures were KOOS score and adverse events.

- Synovial fluid (SF) assessment.
  - SF was collected from patients' knee joints immediately prior to injection and again at 3 months.
  - ELISA for specific biomarkers ADAMTS-4 activity, IL-6, sCD14, MMP1 and MMP3 were performed.
  - A comparative analysis was performed between "responders" and "non-responders". A responder was defined as a patient whose 6-month change from baseline in total WOMAC score exceeded the MIC of 10 points.

Methods

- Patients were recruited prospectively and underwent 6ml injection of Arthrosamid into the knee joint.

- Inclusion criteria
- 1. Radiological OA greater than Kellgren-Lawrence (K-L) grading scale 2
- 2. A knee pain score of greater than 40/100 on a visual analogue scale (VAS).
- 5. No surgery or injection within 12 months.

- Exclusion criteria
- 1. Previous trauma with significant alteration in bone architecture
- 2. Joint re-placement operation on the other knee
- 3. Inflammatory arthritis (i.e., rheumatoid arthritis, spondylarthritis and gout)

Results

- There was a statistically significant improvement in overall scores at 3, 6 and 12 month

Table 1: Mean WOMAC score at each time point and mean difference from baseline

Timepoint	WOMAC (SD)	Difference from baseline (95% CI)	p-value
Baseline	46 (18)	-	-
3 months	30 (22)	15.8 (9.8 To 22.0)	<0.001
6 months	25 (23)	21.1 (15.0 To 27.1)	<0.001
12 months	24 (20)	21.8 (15.6 To 28.0)	<0.001

Mean WOMAC scores are based on the raw values. Mean differences from baseline calculated using general least squares model.

Characteristic	N = 62[1]
Age	56 (50, 60)
Sex	
Female	28 (45%)
Male	34 (55%)
Kellgren Lawrence Score	
1	1 (1.6%)
2	8 (13%)
3	32 (52%)
4	21 (34%)

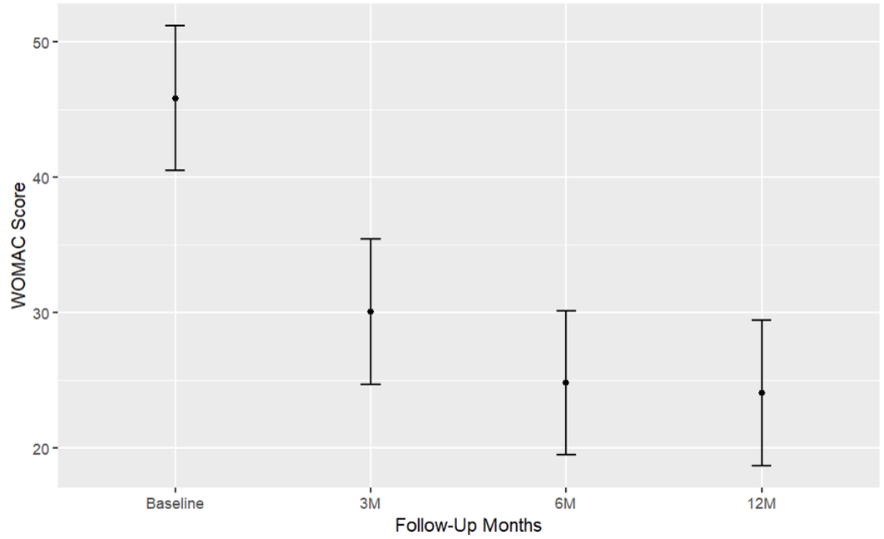

Figure 1: Change from mean baseline WOMAC score over time, with error bars representing 95% confidence intervals.

Results

- There was a statistically significant improvement in overall scores at 3, 6 and 12 month

Table 2: Mean KOOS score at each time point and mean difference from baseline

Timepoint	KOOS (SD)	Difference from baseline (95% CI)	p-value
Baseline	37 (15)	-	-
3 months	54 (21)	16.5 (10.4 To 22.7)	<0.001
6 months	56 (23)	19.5 (13.4 To 25.5)	<0.001
12 months	57 (21)	20.4 (14.3 To 26.6)	<0.001

Mean KOOS scores are based on the raw values. Mean differences from baseline calculated using general least squares model.

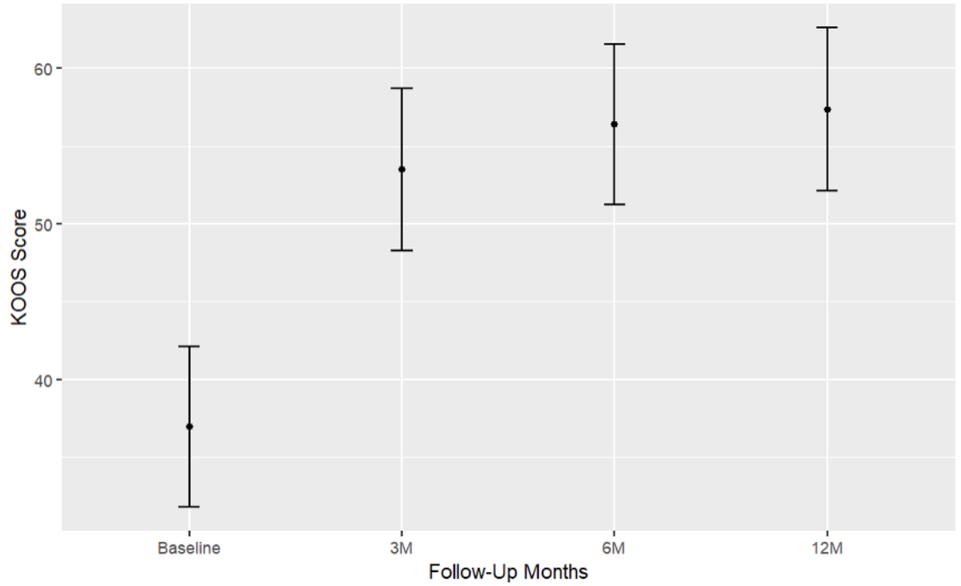

Figure 2: Change from mean baseline KOOS score over time, with error bars representing 95% confidence intervals.

Multivariable generalised least squares analysis of the predictors of 12-month WOMAC Score.

- Worse WOMAC baseline is associated with a worse WOMAC overall score ($p < 0.001$)
- Older age is associated with worse WOMAC overall score ($p = 0.0468$)
- KL score of 3 is associated with worse overall WOMAC score than KL 2 ($p = 0.0291$)
- KL score of 4 is associated with worse overall WOMAC score than KL 3 ($p = 0.0177$)

Synovial Fluid analysis

- Non-detects in the SF were 9% (sCD14), 9% (IL-6), 1% (IL-1RA), 3% (MMP-3), 72% (ADAMTS-4 activity), 0% (HA) and 8% (PRG-4).

- Regardless of outcome, IL1-RA was consistently (94% of samples) elevated in 3-month SFs (Table 1).

	Non-responder			Responder		
Analyte	Baseline Median	3-months Median	Baseline vs. 3-month p-value	Baseline Median	3-months Median	Baseline vs. 3-month p-value
sCD14 (mg/ml)	**0.938**	**1.686**	**0.0105**	1.574	1.875	0.5879
IL-6 (pg/ml)	**75.70**	**134.5**	**0.0771**	71.59	36.81	0.1016
IL-1RA (pg/ml)	**200.5**	**1390**	**0.0078**	**239.1**	**924.5**	**0.0039**
MMP-3 (pg/ml)	**342.1**	**776.8**	**0.0061**	1029	863.6	0.8394

- Proteomic pathway analysis indicates that acute phase response signallinis inhibited after treatment (a pathway regulated by IL-1).

Proinflammatory Phenotype of Arthrosamid® Non-Responders

- Non-responders demonstrated a significant increase in sCD14, MMP-3 and IL-1RA from baseline to 3-months, whereas in responders, only IL1-RA demonstrated a significant increase .
- Multivariable linear regression found no baseline biomarker or other independent variable to be significantly associated with 3-month WOMAC.
- Logistic regression identified higher baseline HA and lower IL-6 to be significantly linked with increased odds of being a responder (p=0.028 and p=0.045, respectively
- Proteomic pathway analysis indicates that APR signalling is activated in non-responders before injection (a pathway regulated by IL-6) (Figure 3B).

Conclusions

- Arthrosamid® injection shows great promise for the relief of symptoms for some patients with established knee OA – 68% demonstrating a meaningful respose at 12 months
- The biomarker shifts in response to treatment presented here have identified a potential IL1-RA mediated mechanism.
- Larger patient cohorts are required to validate findings, further investigate response differences linked to biomarker profiles and establish the potential of biomarker screening for improved patient selection and stratification.