

# The Effectiveness of Alpha-2-Macroglobulin Injections for Osteoarthritis of the Knee

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# Disclosure Information

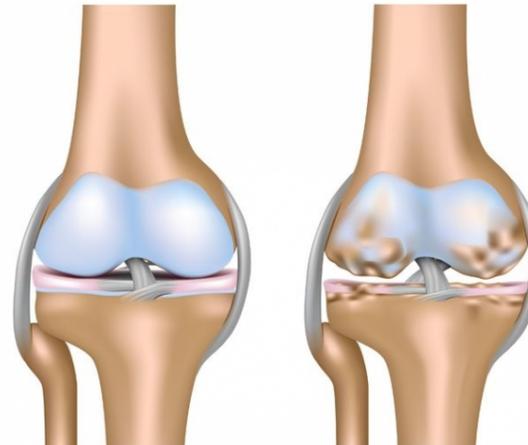
## Research Support

- Plymouth Medical provided the Emcyte FC120 Alpha 2 Macroglobulin (A2M) kits used in the study.
- Arthrex provided the ACP double syringe platelet rich plasma (PRP) kits used in the study.

**All disclosures can be found on the AAOS website.**

# Background

- Osteoarthritis (OA), a degenerative and debilitating joint disease, is one of the most prevalent diseases in the United States.
- Despite the significant burden osteoarthritis can place on an individual and society, nonoperative treatment options are still very limited.
- OA has traditionally been treated with injection of various intraarticular substances producing mixed results.
- Among the choices of injections are corticosteroids, hyaluronic acid, and a growing list of biologics.

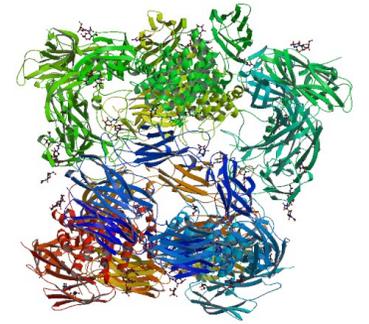


Healthy knee joint

Osteoarthritis

# Background

## Alpha 2 Macroglobulin (A2M)



- Alpha-2-macroglobulin (A2M) is a naturally occurring macromolecule with strong anti-inflammatory properties.
- A2M inhibits the many endogenous and exogenous proteases presenting in the pathogenesis of osteoarthritis.
- A2M blocks the degradation of fibrin to fibrin-breakdown products by deactivating plasmin.
- A2M is not found in high quantities in traditional PRP preparations.
- In several mouse models of OA, A2M administration resulted in lower levels of inflammatory infiltration, synovial hyperplasia, and pro-inflammatory proteases.
- To date, no studies exist evaluating the effectiveness of A2M with other intra-articular injectables.

# Background

## Platelet Rich Plasma (PRP)

- PRP is an autologous blood product made from concentrating the patient's blood sample through centrifugation.
- The concentrated sample is then given as an intra-articular injection.
- The injection contains a concentration of platelets at least two times greater than whole blood product.
- PRP has shown to be equivalent or more effective than corticosteroids, saline and hyaluronic acid.



# Background

## Depo Medrol

- Corticosteroids have been the historical gold standard for injection treatment of osteoarthritis.
- Current data show that corticosteroids are equivalent to PRP, stem-cells, and hyaluronic acid injectables.
- Adverse effects include cartilage breakdown and rare soft tissue effect, such as skin depigmentation, cutaneous atrophy, and fat necrosis.

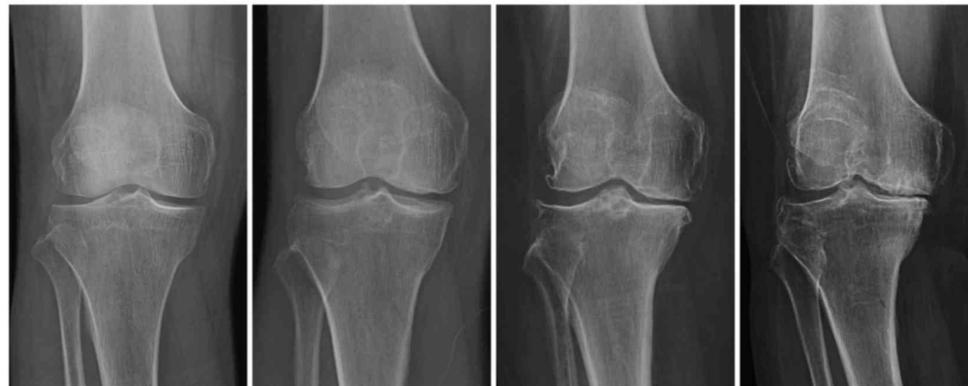


# Purpose

- The purpose of this study is to compare the clinical effectiveness of intra-articular injection of Alpha-2-Macroglobulin (A2M) against both platelet-rich plasma (PRP) and corticosteroids.

# Methods

- This was a randomized, single-center, double blinded study.
- 5 orthopedic surgeons were involved in this study.
- 75 patients with symptomatic knee osteoarthritis with Kellgren-Lawrence grade 2 or 3 were randomized into one of three cohorts receiving intra-articular injection.
- One cohort was given PRP, one cohort was given A2M, and one cohort was given 2 mg of Depo Medrol and 2 mg of Lidocaine .
- All groups had blood drawn to simulate A2M preparation.
- The syringes were prepared by the rep and covered in tape to keep the patient and physician blinded .
- Patients given a PRP or A2M injection ranged between 5 mL and 10mL.

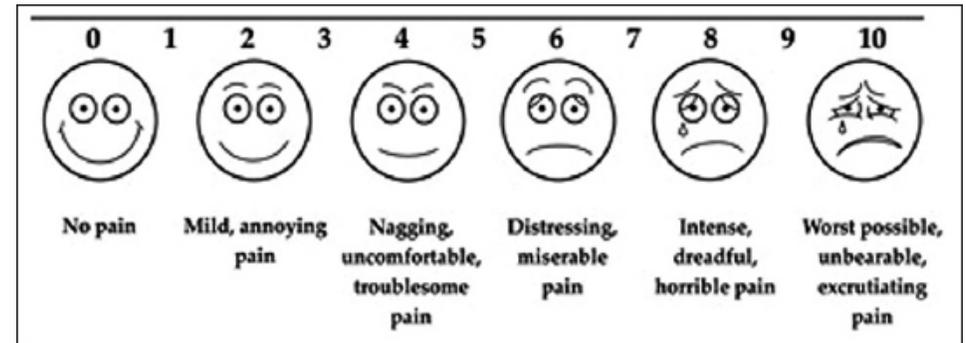


# Methods

- Inclusion criteria:
  - Inclusion criteria included patients greater than 18 years old, with symptomatic OA categorized as KL grade 2 or 3 by the physician
- Exclusion criteria:
  - Pregnant women
  - Systemic or IA injection of corticosteroids in any joint within 3 months before screening
  - Systemic disorders such as diabetes, rheumatoid arthritis, hematological diseases (coagulopathies), severe cardiovascular diseases, infections, or immunodeficiencies
  - Current use of anticoagulant medications or NSAIDs used 5 days before blood donation
  - Surgery on the knee joint within 1 year

# Methods

- Patient reported outcomes (PRO) were collected prior to injection, 6 weeks and 12 weeks following injection.
- The following PRO scores were used:
  - Visual analog scale (VAS)
  - Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)
  - Knee Injury and Osteoarthritis Outcome Score (KOOS)
  - Lysholm
  - Tegner



# Results

- 75 patients were enrolled into the study between June 2018 and February 2019, 25 patients in each cohort
- 7 patients were removed from the study at 6 weeks due to unbearable pain.
- The remaining 68 patients with a mean age of 59.5 years ( $\pm 10.0$ ) and mean BMI of 31.4 ( $\pm 8.7$ ).
- At the final follow-up, 21 patients remained in the A2M cohort, 24 patients in the DM cohort, and 23 patients in the PRP cohort.
- There was no difference between cohorts in age, BMI, sex, ethnicities, smoking, or KL grade.
- There was no difference between the pre-injection score of VAS ( $p = 0.95$ ), WOMAC ( $p = 0.61$ ), KOOS ( $p = 0.89$ ), Lysholm ( $p = 0.47$ ), Tegner level before the injection ( $p = 0.90$ ) or Tegner level before the onset of osteoarthritis ( $p = 0.51$ ).

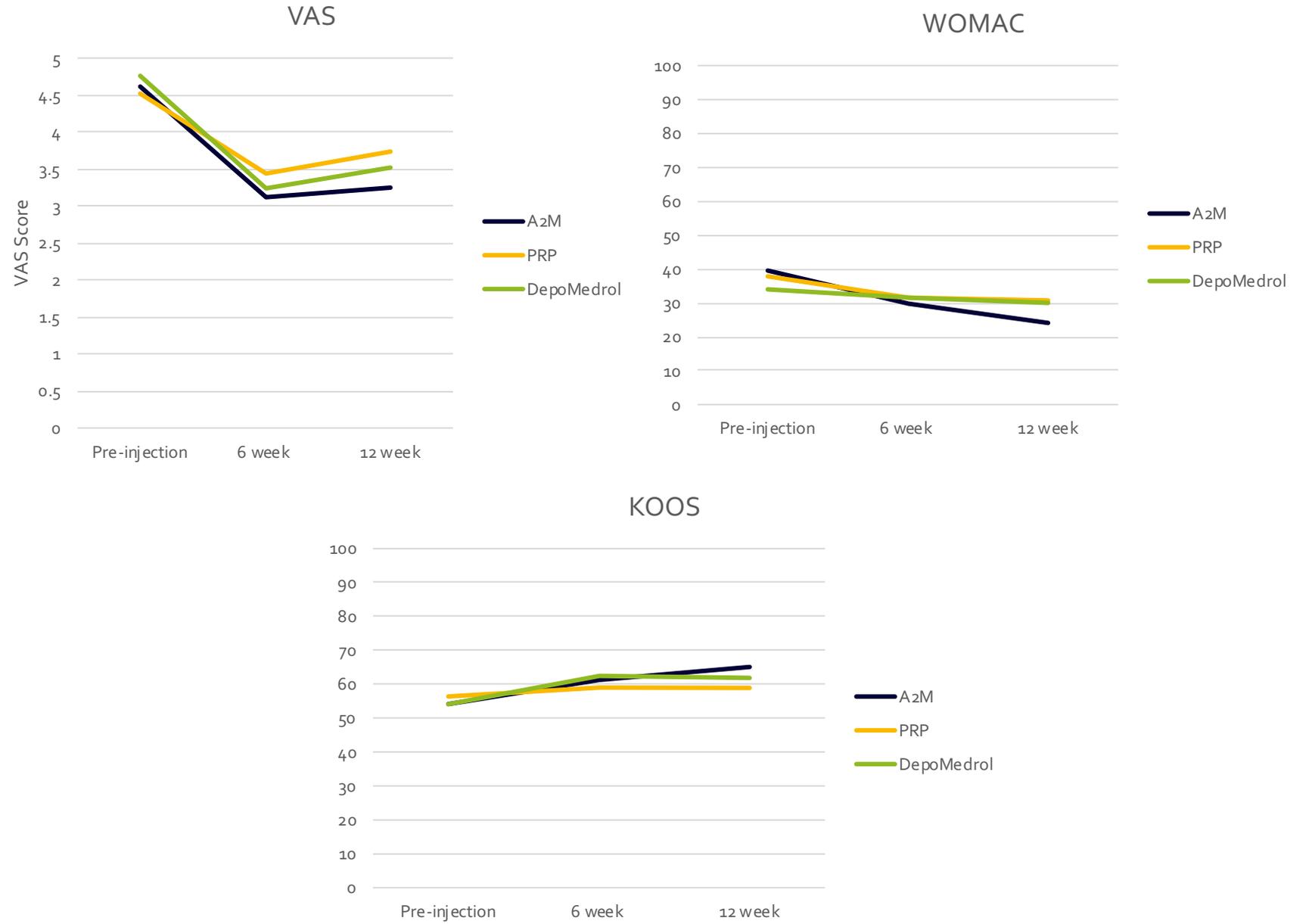
# Results

Patient Demographics				
	A2M (n=21)	PRP (n=23)	Depo Medrol (n=24)	p-value
<b>Age</b>	61.2 ± 8.8	56.2 ± 10.6	59.2 ± 11.2	0.33
<b>BMI</b>	30.8 ± 6.8	31.9 ± 8.9	32.0 ± 8.1	0.38
<b>Sex</b>				
Female	18 (85.7%)	16 (69.6%)	18 (75%)	0.82
Male	3 (14.3%)	7 (30.4%)	6 (25%)	0.54
<b>Ethnicities</b>				
Caucasian	10 (47.6%)	12 (52.1%)	14 (58.3%)	0.88
African-American	6 (28.6%)	6 (26.1%)	6 (25%)	0.97
Hispanic	4 (19.0%)	4 (17.4%)	2 (8.3%)	0.59
Asian	1 (4.8%)	1 (4.3%)	2 (8.3%)	0.83
<b>Smoking</b>				
Yes	0 (0%)	0 (0%)	0 (0%)	1.00
No	17 (81.0%)	15 (65.2%)	16 (66.7%)	0.79
Former	4 (19.0%)	8 (34.8%)	8 (33.3%)	0.57
<b>KL grade</b>				
2	10 (47.6%)	14 (60.8%)	16 (66.7%)	0.70
3	11 (52.4%)	9 (39.2%)	8 (33.3%)	0.60

# Results

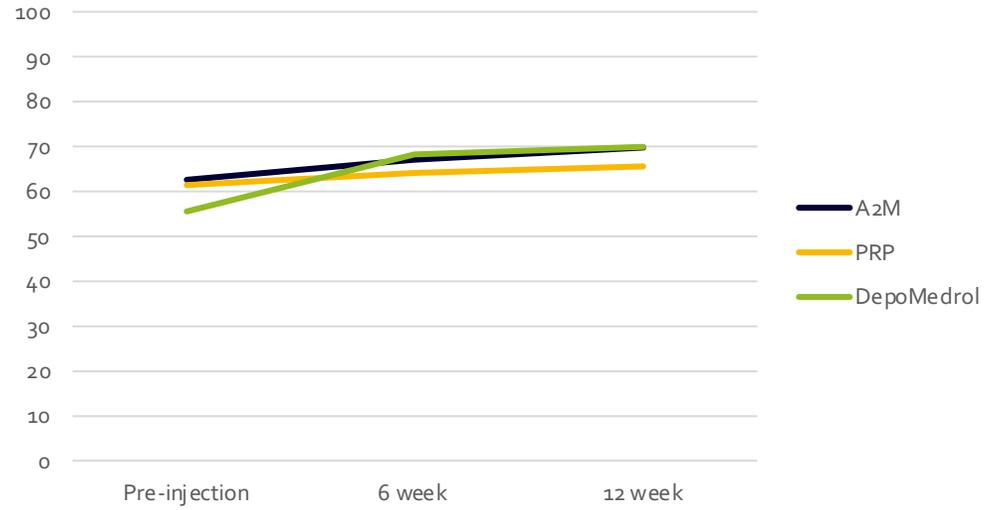
Patient Reported Outcomes				
Pre Injection	A2M	PRP	Depomedrol	p value
VAS	4.6 ± 2.9	4.5 ± 2.7	4.7 ± 3.0	0.95
WOMAC	39.5 ± 22.7	37.8 ± 19.5	34.0 ± 17.5	0.61
KOOS	54.1 ± 21.2	56.4 ± 18.4	54.1 ± 17.7	0.89
Lysholm	62.6 ± 23.5	61.4 ± 19.6	55.5 ± 22.1	0.47
Activity level (Tegner) Before OA	5.2 ± 2.0	5.5 ± 1.8	5.8 ± 2.1	0.51
Activity level (Tegner) pre injection	2.5 ± 1.7	2.6 ± 1.8	2.8 ± 1.6	0.90
<b>6 week</b>				
VAS	3.1 ± 2.7	3.4 ± 2.4	3.4 ± 3.0	0.91
WOMAC	29.6 ± 20.2	29.6 ± 20.2	29.6 ± 20.2	0.94
KOOS	61.1 ± 21.1	59.0 ± 19.1	62.4 ± 23.3	0.85
Lysholm	67.2 ± 22.5	64.2 ± 22.2	68.0 ± 24.1	0.83
Tegner	2.7 ± 1.4	3.0 ± 2.1	3.0 ± 1.7	0.73
<b>12 week</b>				
VAS	3.2 ± 2.6	2.7 ± 1.4	2.7 ± 1.4	0.80
WOMAC	24.1 ± 23.1	30.7 ± 19.0	27.5 ± 22.3	0.59
KOOS	65.1 ± 25.4	58.7 ± 19.1	60.7 ± 26.0	0.66
Lysholm	69.7 ± 24.1	65.6 ± 19.1	71.6 ± 20.5	0.68
Tegner	3.4 ± 2.1	3.4 ± 2.1	3.3 ± 2.1	0.94

# Results

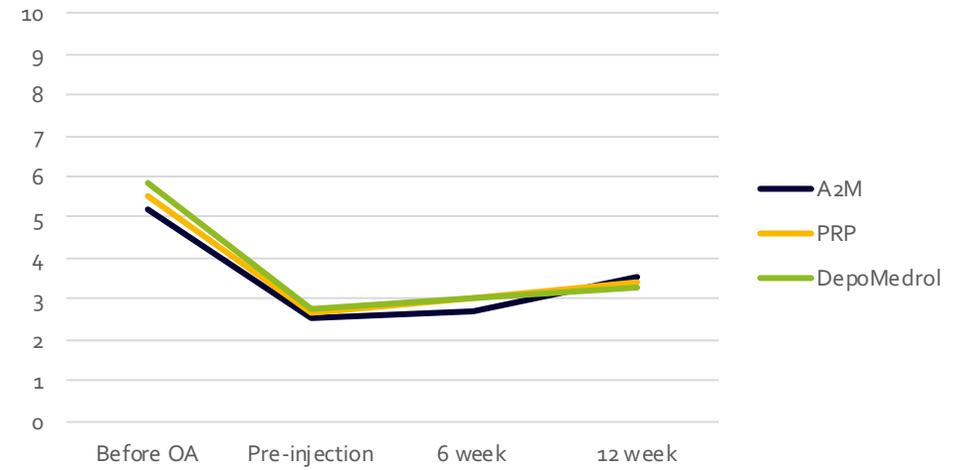


# Results

## Lysholm



## Tegner



# Results

- At 6 weeks, the A2M group had the greatest improvements in VAS ( $-0.2 \pm 3.2$ ), WOMAC ( $-7.3 \pm 17.8$ ), and Lysholm ( $-8.0 \pm 22.5$ ) scoring, however, the differences were not statistically significant.
- Between the injection and the 12 week visit, the A2M group had a statistically significant improvement in WOMAC score compared to PRP and Depo Medrol ( $-18.4$  v  $-5.7$  v  $-7.1$ ,  $p = 0.03$ ).
- Overall, both Depo Medrol ( $-1.5 \pm 3.5$ ) and A2M ( $-1.8 \pm 3.0$ ) had a better improvements in VAS when compared with traditional PRP ( $-0.6 \pm 2.1$ ). However, this difference was also not statistically significant.

# Results

Mean Difference In Patient Reported Outcomes Between Office Visits				
Difference Between pre injection and 6 weeks				
	A2M	PRP	Depomedrol	p value
VAS	-1.6 ± 2.4	-1.2 ± 2.6	-1.5 ± 3.0	0.84
WOMAC	-10.9 ± 22.7	-7.0 ± 17.1	-0.7 ± 25.7	0.27
KOOS	7.9 ± 21.6	2.9 ± 20.2	8.3 ± 22.5	0.59
Lysholm	5.6 ± 16.0	2.7 ± 19.7	12.5 ± 24.1	0.23
Tegner Before (OA)	-2.0 ± 2.3	-2.7 ± 2.0	-2.4 ± 2.6	0.56
Tegner Before Injection	0.2 ± 1.2	0.2 ± 1.4	0.3 ± 1.5	0.98
Difference between 6 and 12 weeks				
VAS	-0.2 ± 3.2	0.6 ± 2.2	0.0 ± 3.7	0.73
WOMAC	-7.3 ± 17.8	1.3 ± 18.0	-4.0 ± 26.7	0.34
KOOS	-5.3 ± 21.1	-2.4 ± 16.6	-6.0 ± 20.5	0.76
Lysholm	-8.0 ± 22.5	-0.9 ± 17.9	-3.7 ± 18.2	0.24
Tegner	0.3 ± 1.9	0.3 ± 1.9	-0.04 ± 1.6	0.79
Difference between pre injection and 12 weeks				
VAS	-1.8 ± 3.0	-0.6 ± 2.1	-1.5 ± 3.5	0.36
WOMAC	-18.4 ± 20.5	-5.7 ± 15.2	-7.1 ± 22.2	0.03
KOOS	2.9 ± 31.9	0.9 ± 14.9	3.0 ± 30.8	0.96
Lysholm	-2.1 ± 29.3	-1.8 ± 1.8	-2.2 ± 2.6	0.33
Tegner	0.5 ± 2.0	0.5 ± 1.8	0.2 ± 2.1	0.85

# Limitations

- Small study because of cost of A2M and PRP kits.
- Unequal ratio of male to female patients.
- Onset of pain relief and viscosities of A2M, PRP and Depo Medrol are different, potentially causing response bias if patients tried to guess which treatment they received.



# Conclusion

- Our study demonstrates Alpha-2-Macroglobulin decreased arthritic symptoms more than traditional PRP and Depo Medrol.
- Both A2M and corticosteroids appear to show better effectiveness than traditional PRP injection, however the differences are small and did not reach statistical significance in most outcome measures.
- The extra preparation time required and cost associated with A2M may not warrant its routine use in the management of knee osteoarthritis.

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