

NEW STUDIES USING INTRA-ARTICULAR POLYGLYCAN FOR OSTEOARTHRITIS IN HORSES



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MEDICATIONS

- Now tailored to influence any tissue
- Applications by a number of routes
 - Systemic
 - Topical
 - Intra-articular
 - Physical



CHOICES



AIMS OF THERAPY

- Remove inciting cause
- Decrease catabolic state
(inflammation)
- Increase anabolic state
- Return to best possible use



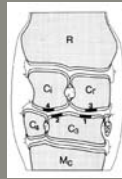
GROWING COMPLEXITY OF THERAPIES

- Objective, experimental testing often lags behind development and commercialization
- Therapeutics now showing specific effects
 - SMOADS – Symptom-modifying OA Drugs
 - DMOADS – Disease-modifying OA Drugs
 - Combination

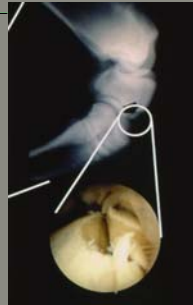
Methods of Action

- Symptom modifying effects
 - SMOAD - Symptom Modifying Osteoarthritic Drugs
 - Improve symptoms of disease
 - Anti-inflammatories
 - Pain modifying
- Disease modifying effects
 - DMOAD – Disease Modifying Osteoarthritic Drugs
 - Chondroprotective
 - Increase anabolic effects, decrease catabolic effects

Osteochondral Fragment Model



Middle Carpal Joint



Clinical Examination - Weekly

- Lameness examination
 - 0 – 5 AAEP Scale
- Synovial Effusion
 - 0 – 4 Scale
- Response to Flexion
 - 0 – 4 Scale

Biomarkers - Weekly

• Serum Biomarkers

- Articular cartilage Biomarkers
 - GAG, CS846, CPII, C1,2C, Col II
- Bone Biomarkers
 - Osteocalcin, CTX1, BAP, Col I

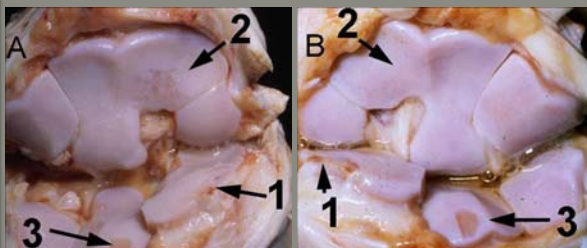
• Synovial Fluid Biomarkers

- Inflammation
 - Total Protein, WBC, PGE2, IL-1
- Articular cartilage and Bone as above

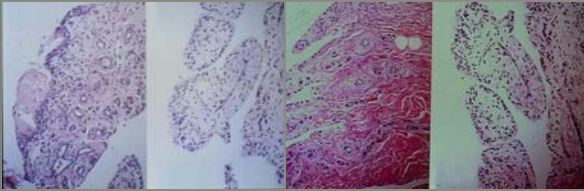
Imaging



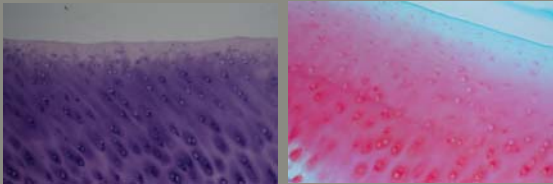
Gross Lesions



Synovial Membrane Histology



Articular Cartilage Histology



Miscellaneous Parameters

- Articular Cartilage Matrix Metabolism
 - GAG content and GAG Synthesis
 - Collagen content
- Molecular Characteristics
 - Inflammatory enzyme up- and down-regulation
 - Articular Cartilage and synovial membrane

Evaluation of Treatments in Equine OA Model

- IV HA
- IA betamethasone esters
- IA triamcinolone acetonide
- IA methylprednisolone acetate
- Ad IL-1ra
- Pentosan polysulfate
- Shockwave therapy
- IM Adequan™
- Oral HA (Conquer)
- Orthokine™
- Oral Avocado-Soya (Vetoquinol)
- Surpass
- Stem cells (Fat and BMDSC)
- Tiludronate
- IA Adequan
- IA HA
- IV and IA Polyglycan

Routes of Administration

- Systemic
 - Antiinflammatory
 - Antiresorptive
 - Chondroprotective (?)
- Intraarticular
 - Antiinflammatory
 - Growth Factors (?)
 - Stem cells
 - Device (?)
- Physical
 - ESWT
- Topical

Route of Non-Corticosteroid Administration

Product	Intra-articular	Intra-venous	Intra-muscular
Polysulfated Glycosaminoglycan (Adequan)	55/764 (7.2%)	34 (4.5%)	643/764 (84.2%)
Sodium hyaluronate (Legend)	113/764 (14.8%)	589/764 (77.1%)	10/764 (1.3%)
Sodium hyaluronate (Hylartin V/Hyvisc)	635/764 (83.1%)	13/764 (1.7%)	1/764 (0.1%)
Sodium Hyaluronate (Map-5)	150/764 (19.6%)	64/764 (8.4%)	4/764 (0.5%)
Hyaluronic acid/sodium chondroitin sulfate/N-acetyl-D-glucosamine (Polyglycan)	69/764 (9.0%)	190/764 (24.9%)	57/764 (7.5%)

Polyglycan



- Combination of (2.5 ml):
 - 12.5 mg Sodium Hyaluronate
 - 250 mg Sodium Chondroitin Sulfate
 - 250 mg N-acetyl-D-Glucosamine
- IA use licensed as intra-op lavage / device

COMBINATION THERAPY

- Sodium Hyaluronate
 - Safe and efficacious in human OA
 - Conziet and Chevalier, 2008; Conrozier, et al, 2009
 - Safe and efficacious in osteochondral fragment model
 - Frisbie, et al, 2009
 - Some form of reaction in 7 – 53% of humans
 - Conrozier and Chevalier, 2008; Cohen, et al, 2008; Huskin, et al, 2008; Migliore, et al, 2008; Witteveen, et al, 2008
 - Is product-specific
 - Reichenbach, et al, 2007
 - Case report of severe reaction in a horse 10 hours after injection
 - Kuemmerle, et al, 2006

COMBINATION THERAPY

- N-acetyl-D-glucosamine
 - IA administration significantly better than IM NAG and IA sodium hyaluronate in a rabbit model
 - Shikhman, et al 2005
- Additive effects in vitro when combined with chondroitin sulfate
 - Dechant, et al, 2005

INTRODUCTION OF NEW PRODUCT

• Safety Study

- Need to be assured that there are no systemic or local effects
- Usually test at recommended doses and higher doses to assure safety

• Efficacy Study

- Evaluate in either naturally-occurring disease or model of intended disease
- Model allows for strict study design and minimizes outliers

SAFETY STUDY

• 24 horses free of orthopedic disease

- 1 middle carpal joint – uninjected control
- Opposite middle carpal joint
 - 8 horses - 2.5 ml isotonic saline
 - 8 horses – 2.5 ml GHCS
 - 8 horses – 7.5 ml GHCS
- Saline and 2.5 ml GHCS administered on days 0, 7 and 14
- 7.5 ml administered only on day 0 and evaluated on days 1, 3, 5 and 7
- Other groups evaluated on days 1, 3, 5, 7, 14 and 21

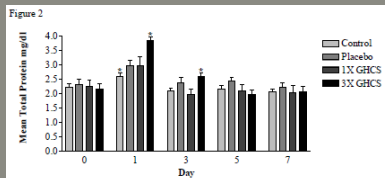
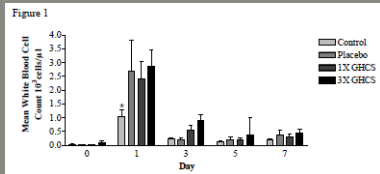
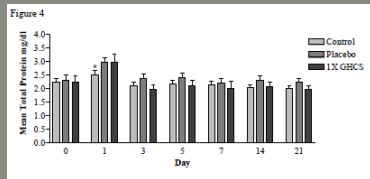
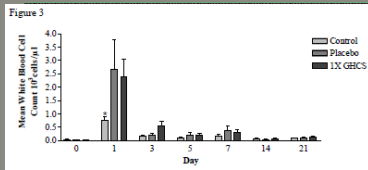
SAFETY STUDY

• Outcomes

- Clinical examination
 - Lameness, effusion, response to flexion
- SF WBC and TP

• Results

- No effects on clinical examination
- Needle aspiration alone increased SF WBC and TP
- 2.5 ml saline or GHCS increased SF WBC and TP above aspiration at 1 day.
- 7.5 ml GHCS increased SF TP for 3 days
- All values returned to baseline



SAFETY STUDY - CONCLUSION

- Presence of fluid, regardless if treatment or control, increased synovial fluid WBC and TP levels beyond those of aspiration
- 3X GHCS increased TP levels significantly higher for an additional 2 days.
 - No saline volume control
 - Increased IA volume in normal or acutely damaged joints have no significant long-term effect

LAMENESS I

Assessment of Intravenous or Intra-articular Hyaluronic Acid, Chondroitin Sulfate, and N-acetyl-D-glucosamine in Treatment of Osteoarthritis Using an Equine Experimental Model

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- AAEP 2009



Assessment of IA or IV Hyaluronic Acid, Chondroitin Sulfate And N-acetyl-d-glucosamine (Polyglycan®) in Treatment of OA using an Equine Experimental Model

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- Conflicts of interest
 - None



Approaching Joint Disease

Goals

- Reduce pain (SMOAD)
- Minimize further deterioration (DMOAD)

Therapeutic Plan

- Accurate diagnosis
- Severity
- Available rest period
- Economic limitations
- Minimize side effects
- Choose the therapeutic substance



Introduction

Numerous therapeutic options

- 19 evaluated using similar model OA

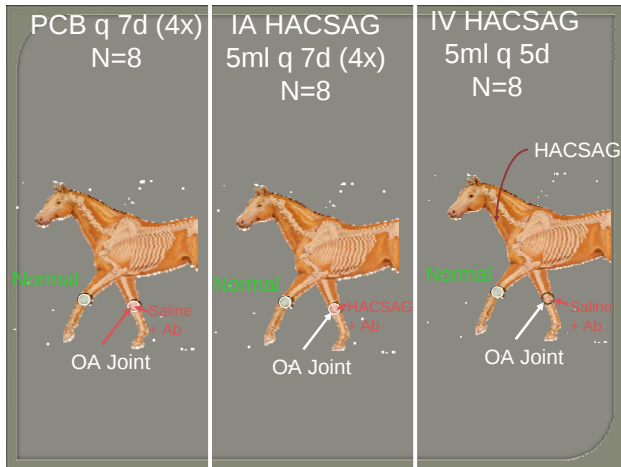
Polyglycan® (5ml)

- Hyaluronic acid sodium salt, 25mg
- Sodium chondroitin sulfate, 500mg
- N-acetyl-D-glucosamine, 500mg
- Labeled IA post surgical lavage & replacement of synovial fluid
- Principal intended MOA – mechanical

Introduction

- Doses in the market, ~750,000
- Safety
 - US Manufactured cGMP compliant FDA approved facility
 - IV/IM Caldwell, et al, 2006 (unpublished)
 - IA Kawcak, et al, 2008 (unpublished)
- Anecdotal reports of efficacy
- Field use IV/IA (*Ferris, et al 2009 AAEP*)

*Not marketed or approved as a drug

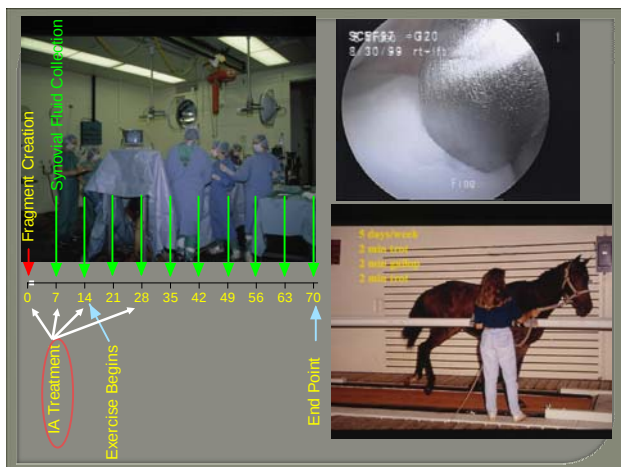


Antimicrobial Use

Always	341/738	46.2%
Occasionally	239/738	32.4%
No or Never	158/738	21.4%

Respondents practicing
<10 years were
significantly ($p = .0001$)
more likely to use
amikacin

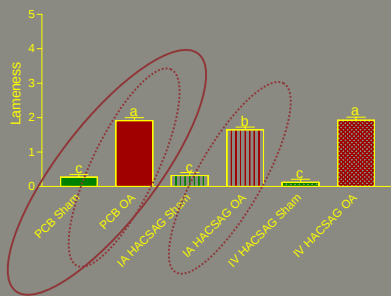


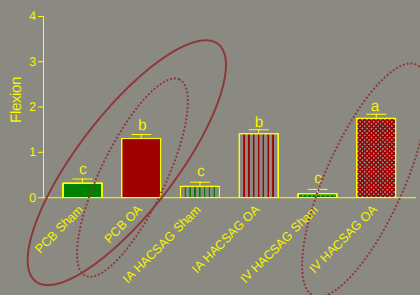
In Vivo - OA Model

- Clinical
 - Musculoskeletal exam
 - Radiographic
- Synovial fluid analysis
- Gross
- Histology
 - Synovial membrane
 - Articular Cartilage
- Biochemical
 - Synovial fluid
 - Cartilage
- Stats
 - Proc GLIMMIX
 - Main effects of treatment & OA, time when applicable
 - Interactions
 - LSM $\pm$ SEM
 - $P < 0.05$

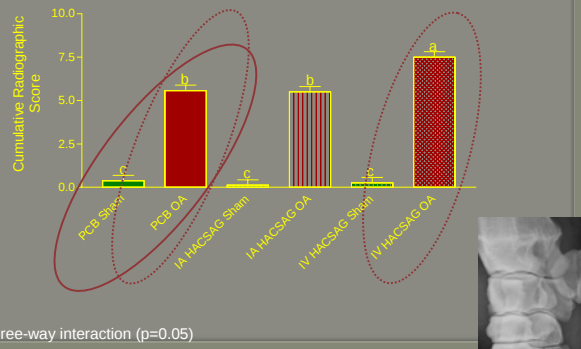
Results: Lameness Score



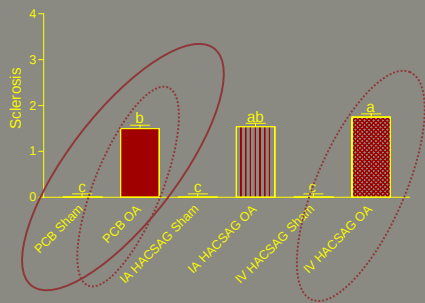
Results: Flexion Score



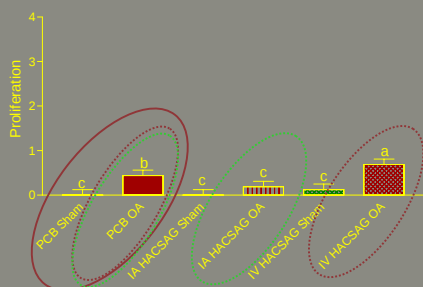
Results: Radiographic- Total



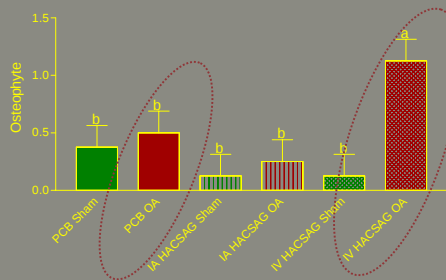
Results: Radiographic- Sclerosis



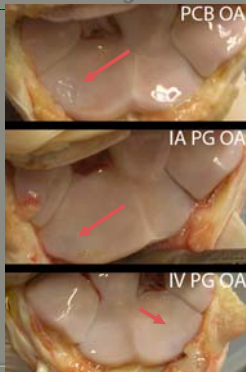
Results: Radiographic- Proliferation



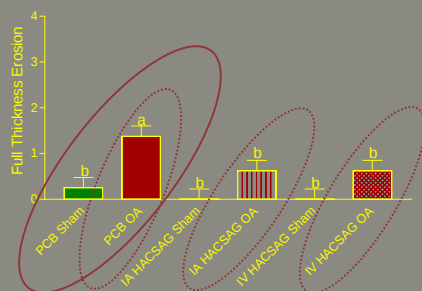
Results: Radiographic- Osteophyte



Results: Gross Joint Observation



Results: Gross Joint Observation



Main effect of Treatment ($p=0.06$)

IA Summary:

- SMOAD
- DMOAD
 - Radiographic - Proliferation
 - Gross OA



IV Summary:

- DMOAD
 - Gross OA
- Questions/Concerns
 - Flexion
 - Radiographic change
 - Proliferation
 - Sclerosis
 - Osteophyte
 - Assumption of biologic activity - IV

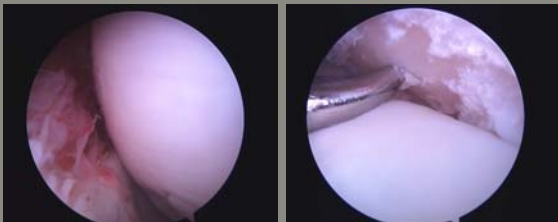
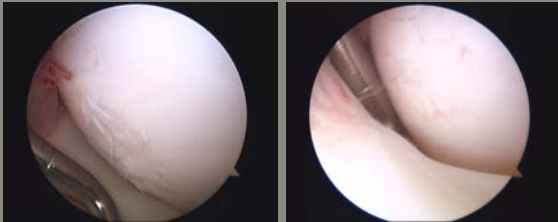


Imaging



Conclusions:

- IA Polyglycan should result in beneficial effect on equine OA
- Dose regiment ?
- Clinical studies to further define case selection/dose
- New modified IV study
 - TX starting Day 14
 - IV Control: No IA saline/amikacin





Medical Devices

A White Paper on Medical Devices in Equine Medicine

Developed by the
Biological and Therapeutic
Agents Committee