Concepts of Cartilage Facilitation and Protection with PRP and Biologics in the Athlete
Bert R. Mandelbaum MD DHL (hon)
FIFA Medical Committee
CONCACAF Chair Medical Committee
Asst Medical Director MLS
F-MARC Member
Team Physician US Soccer, LA Galaxy, Pepperdine University

Biologics PRP/Stem Cells and more
Purpose of this talk

- How it all works?
  - Mechanisms of action
- Is it effective?
  - In who and when?
- Is it cost effective?

Disclosures

- Consultant
  - Arthrex (Royalties)
  - JRF
  - Johnson and Johnson and Depuy
  - Mitek
  - Exactech
  - Geistlich
  - Regen Labs
  - Vericel
  - Alter G
  - BioMarin

“Chondroprotection and Chondrofacilitation”

Biologic Organ Spectrum of approaches to the Knee

- Synovium and joint Milieu
  - cytokines, factors, hormones,
- Articular Cartilage Resurfacing
  - < 2 cm2 > 2 cm2 size matters!
- Osteochondral defects
  - < 7 mm deep
  - > 7 mm
- Bone marrow lesions
  - Subchondral Edema (SCE)
  - Osteonecrosis (AVN)
  - Insufficiency Fractures (ISFX)
  - SONK

Static and Dynamic Malalignment, Instability, Meniscal Pathology must be managed!
Evolving Concept…. “Chondropenia”

The Journey

• Loss of volume articular cartilage

Orthobiological Opportunity
Concepts and Technology
Chondrofacilitation

• To avoid surgery
• To prep for surgery aspirate or reduce inflammation
• Adjunct during surgery…
• Adjunct after we operate early and late
• Disease modify OA
• Cost effective ICER, QALY, WTP
• Reduce incidence of TKR
The Regenerative Tissue Engineering Triad

- Cells
- Growth factors and Cytokines
- Scaffolds/Biomaterials

Chondroprotection and Chondrofacilitation
Performance Enhancing Adjuvants (PEAs)

- GS/CS
- Hyaluronic Acid Injection
- PRP
- Cytokine Modulation
  - IL-1Ra Inhibition of Inflammatory Response
- Stem Cells
  - Adipose derived
  - BMAC
  - Allogeneic stem cells
  - Induced pluripotential cells
- Amniotic Fluid
- Estrogens

What is the ideal adjuvant combination?

Chondroprotection and the Prevention of Osteoarthritis Progression of the Knee
A Systematic Review of Treatment Agents
Gallagher, Ciccotti et al 2015

GS/CS may protect joint cartilage and delay OA progression
Hyaluronic acid injections showed variable efficacy

Glucosamine /Chondroitin Sulfate
Monosaccharide precursor to GAG

Clinical Evidence

- GAIT Study NIH 2006
  - Beneficial to less severe
  - 2000 mg vs. placebo
  - 88% improved vs. 17% placebo
  - KOOS and KPS better
- RCT Reginster Lancet 2001
  - Improvement of WOMAC scores
  - Decrease in X-ray OA
  - Chondroprotective
- RCT Pavelka Ann Int Med 2000
  - Less JSN
  - Better subjective scores

Mechanism of Action

- Synergistic increased PG production and dec in degradative enzymes
- Lipello Clin Orthop 2000
  - inhibition IL-1Beta and TNF-alpha, NO and PGE2 production in human Chondrocyte
  - Shikman et al J Immunol 2001
  - increases GAG content and cartilage thickness after injury
  - Degenar ORS 2001)

Hyaluronic Acid

- Rationale
  - Physiological and GAGs bind to collagen mesh and aid in hydration
  - Biomechanical: HA is for shock absorption and lubrication...aging and OA concentration and MW

- Therapeutic Response
  - Decrease inflammatory response and improve viscoelastic properties
- (Abatangelo ’89 Clin Ortho. Rel Res.)
  - chondrocyte density, territorial matrix, metabolism
- ( Guidolin et al OA Cartilage 2001)
  - Protects cartilage degeneration after meniscectomy
  - Enhances synthesis of GAGs
- ( Ameil ORS 2001)

32 Published or presented Clinical Trials for OA

- 6 Supartz-Japan
- 6 Healon-United States
- 13 Hyalgan-France/Italy
- 7 Synvisc- North America

In the past year significant number of presented studies.

Conclusion

- Intra-articular hyaluronan/hylan is superior to placebo in relieving symptoms associated with OA.
  (Wobig 98 Marshall 97)
- Produced similar results as NSAIDs and Corticosteroids.
  Lasting appx. 6 months (Dickson 98, Adams 95)
- Treatment is well tolerated and safe. (Lussier 96 Kotz 99)
Growth factors: Function

- **PD-EGF** (platelet-derived epidermal growth factor)
  - Cell growth, recruitment, Differentiation, skin closure, Cytokine secretion

- **PDGF A + B** (platelet-derived growth factor)
  - Potent cell growth, recruitment
  - Blood vessel growth, granulation
  - Growth factor secretion; matrix formation with BMPs (collagen and bone)

- **TGF-β1** (transforming growth factor)
  - Blood vessel (±), collagen synthesis, Growth inhibition, apoptosis (cell death), Differentiation, activation

- **IGF-I, II** (insulin-like growth factor)
  - Cell growth, differentiation, recruitment
  - Collagen synthesis with PDGF

- **VEGF, ECGF** (vascular endothelial growth factor, endothelial cell growth factor)
  - Angiogenesis, Mitogenesis, Cell growth, migration, new blood vessel growth
  - Anti-apoptosis (anti–cell death)

- **bFGF** (basic fibroblast growth factor)
  - Chemotaxis, Cell growth, Cell migration, blood vessel growth

Growth factors positive effect cartilage metabolism and regeneration
Synovium, Meniscus, chondrocytes

- Akeda K et al. Osteoarthritis Cartilage. 2006

**PRP** 1507 unique proteins in platelets

**GROWTH FACTORS** | **FUNCTION**
---|---
**PD-EGF** | Platelet-derived epidermal growth factor |
**PDGF A + B** | Potent cell growth, recruitment, angiogenesis |
**TGF-β1** | Transforming growth factor |
**IGF-I, II** | Insulin-like growth factor |
**VEGF, ECGF** | Vascular endothelial growth factor, endothelial cell growth factor |
**bFGF** | Basic fibroblast growth factor |

**Results:**
- PRP stimulates proliferation in cells derived from articular cartilage, synovium, and ACL
- Enhanced SZP secretion from synovium- and cartilage-derived cells.
- High loads and low sliding speeds PRP decreased the friction coefficient
- Conclusion: PRP significantly stimulates cell proliferation and SZP secretion by articular cartilage and synovium of the human knee joint. Furthermore, PRP contains endogenous SZP and, in a functional bioassay, lubricates bovine articular cartilage explants.

How does PRP work???

**ACP Excludes WBCs**

Growth factor and catabolic cytokine concentrations are influenced by the cellular composition of platelet-rich plasma

- MMP-9 and IL-1 β measured within ACP (PRP-1) and Biomet (PRP-2)
  - Neutrophil-derived MMP-9 known to degrade collagen, causes poor healing
  - IL-1 β is primary cytokine for inflammation and matrix degradation
- Values correlated with WBCs (very minimal amount measured in ACP)

**ACP** Excludes WBCs

WBC and MMPs

WBC and matrix synthesis

“More WBC more genes catabolic”

**Anabolic:Catabolic** | **Platelet Concentration** | **WBC Concentration**
---|---|---
| r | r² | p | r | r² | p |
**COL1A1:COL3A1** | 0.79 | 0.62 | <0.01 | -0.55 | 0.30 | <0.01 |
**COMP** | 0.73 | 0.53 | <0.01 | -0.40 | 0.16 | <0.01 |
**MMP-3** | 0.37 | 0.14 | <0.01 | 0.65 | 0.42 | <0.01 |
**MMP-13** | -0.76 | 0.58 | <0.01 | 0.45 | 0.20 | <0.01 |

McCarrel & Fortier, JOR, 2010

**Stimulation of the Superficial Zone Protein and Lubrication in the Articular Cartilage by Human Platelet-Rich Plasma**

Sakata, Reddi et al 2015

- Lubrication properties pin-on-disk tribometer.
- Results: PRP stimulates proliferation in cells derived from articular cartilage, synovium, and ACL
- Enhanced SZP secretion from synovium- and cartilage-derived cells.
- High loads and low sliding speeds PRP decreased the friction coefficient
- Conclusion: PRP significantly stimulates cell proliferation and SZP secretion by articular cartilage and synovium of the human knee joint. Furthermore, PRP contains endogenous SZP and, in a functional bioassay, lubricates bovine articular cartilage explants.

How does PRP work???
Platelet-Rich Plasma Use in Knee Osteoarthritis
2016
A Systematic Review of Randomized Controlled Trials
Benjamin J. Sherman†, James P. Bradley‡, Neal El Attrache, Tim Foster, Bert R. Mandelbaum§
From †Western University of Health Sciences, Pomona, California
‡Center for Sports Medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, Kerlan Jobe Clinic
§Santa Monica Orthopaedic and Sports Medicine Research Foundation, Santa Monica, California

PRP in RCTs demonstrates significant benefit in low level OA

Therapies – Platelet rich plasma Evidence Based Medicine


Several studies comparing HA and PRP effectiveness have been found. In knee OA treatment, PRP has major effectiveness more than HA (Kon et al, 2011, Filardo et al, 2011, Sanchez et al, 2012, Spakova et al 2012, Cerza et al., 2012, Raeissadat et al, 2015).

The results of several meta-analyses confirm the major effectiveness of PRP (Khoshbin et al, 2013, Chang et al. 2014, Laudy et al, 2014, Campbell et al, 2015).

Chondropenia/Early OA
PRP vs Placebo
Patel et al AJSM 2013

- 78 pts Single PRP vs 2 inj
- PRP vs NS
- WOMAC
- PRP Both groups p<0.001
- Knees with Ahlback grade 1 fared better than those with grade 2.

Chondropenia/Early OA
PRP vs HA

- Better improvement after PRP injections for younger patients
  - < 60 y/o 65% improvement
  - >60 y/o 30% improvement

Best Results PRP>HA younger less severe degeneration
Chondropenia/Early OA

PRGF vs. HA RCT multicenter
A randomized clinical trial evaluating plasma rich in growth factors (PRGF-Endoret) versus hyaluronic acid in the short-term treatment of symptomatic knee osteoarthritis
Sánchez et al Arthroscopy 2012

- 176 pts
- Both groups statistically improved over baseline
- PRGF (single spin) low WBC was higher in all outcome measures by 14.1% although no significant differences were found!

ACP vs HA RCT
Comparison Between Hyaluronic Acid and Platelet-Rich Plasma, Intra-articular Infiltration in the Treatment of Gonarthrosis
Cerza et al AJSM 2012

- 120 pts
- 4 injections
- continuously improving up to 24 WOMAC ACP>HA P< 0.001
- Pts with Grade III OA worse in HA group no different in ACP group

Autologous Interleukin-1 receptor antagonist improvements RCT in OA
Yang et al Osteoarthritis and Cartilage 2008

- In theory? Incubation with CrSO₄-coated glass beads stimulates the synthesis of anti-inflammatory cytokines, interleukin-1 receptor antagonist (IL-1ra)
- 176 pts at 1 year
- WOMAC NSD
- KOOS improved symptom P< 0.002 and Sport p< 0.04 Domains
- Efficacy maybe not as robust as PRP!!!

ORTHOKIN Utrecht Holland

I will have what Kobe had???

Chondroprotection and Chondrofacilitation...
Performance Enhancing Adjuvants (PEAs)
Bert R. Mandelbaum MD DHL

- GS/CS
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- PRP
- Cytokine Modulation
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What is the ideal adjuvant combination?

Hyaluronic acid induces the release of growth factors from platelet-rich plasma
Lio et al Asia Pacific Sports Med and Arthroscopy 2016

- HA and PRP

What is the ideal adjuvant combination?
What is the ideal adjuvant combination?

- HA and PRP
- attenuate cartilage degeneration in ACLT-OA animal model
- regenerative and anti-inflammatory agents for future clinic OA therapy.

Synergistic anabolic actions of hyaluronic acid and platelet-rich plasma on cartilage regeneration in osteoarthritis therapy
Chen et al Biomaterials 2014

Chondroprotection and Chondrofacilitation..
Performance Enhancing Adjuvants (PEAs)
Bert R. Mandelbaum MD DHL

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What is the ideal adjuvant combination?

Treatment of Knee OA With Autologous Mesenchymal Stem Cells: A Pilot Study
Orozco et al Transplantation 2013

- 12 pts Barcelona
- BMAC
- Significant improvement in VAS, WOMAC
- 27% improvement of T2 MRI

Minimal Evidence for stem cells… lots for PRP!

Intra-Articular Injection of Mesenchymal Stem Cells for the Treatment of Osteoarthritis of the Knee: A Proof-of-Concept Clinical Trial
Jo et al 2014 Seoul, Korea

- 18 pts Adipose MSC
  1.0 x 10^8th high vs. low dose
- WOMAC at 6 months
- Improvements no stats yet!

Minimal Evidence for stem cells…
Treatment of Knee OA With Allogeneic Mesenchymal Stem Cells:
RCT
Vega et al Transplantation 2015 Vallalolid, Spain

- 30 pts
- randomized allogeneic with 40 × 10^6 cells. vs. HA
- 38% to 42% improvement in pain compared to 10% to 14% in active controls with hyaluronic acid

A randomized, double-blind, controlled study of adult human mesenchymal stem cells delivered via intra-articular injection to the knee joint following meniscectomy

C. Thomas Vangsness Jr., MD, David Fox, MD, David Dellaero, MD, David Griffin, MD, Jack Farr, MD, Joel Boyd, MD, John O’Donnell, MD

Amniotic fluid stem (AFS) cells
- amniocentesis week 14 - 20
  ultrasonography chromosomal analysis and levels of alpha fetoprotein
- AFS cells generated by selecting for ckit positive cells and single cell cloning
  can be expanded in vitro differentiated into cells of all three embryonic germ layers

Interim Analysis of Prospective, Multi-Center Outcome Observational Cohort Registry of Amniotic Fluid Treatment for Osteoarthritis of the Knee 2015 Report
Douglas Beall, MD and Sri Nalamachu, MD

- Amniovisc
- first 181 patients in a Registry Study designed for 470 patients suggest that use of a processed amniotic fluid allograft may offer a safe and effective treatment for osteoarthritis

Social and Economic Impact
Landi et al 2016

The steady increasing year after year of surgery incidence will lead cost to grow (Piscitelli et al, 2004, Chen et al, 2012) for the foreseeable future (Hiligsmann et al., 2013, Culliford et al, 2015).

In Italy 2001: 26,697  2007: 51,971  2014: 65,000

Source: Riap, Italian Arthroplasty Registry Project
ICER plane

Incremental Cost effectivenes Ratio

![ICER plane](image)

ICER (Incremental Cost Effectiveness Ratio): €1,524.15/QALY

Probabilistic Sensitivity Analysis

PSA

Cost Effectiveness Acceptability Curve – CEAC

WTP €30,000 – 82% iterations are cost-effective

Conclusions

- PRP-based therapy, obtained with is a cost-effective therapy with respect to i.a. HA in the 1 year scenario.
- TKR incidence reduced from 1.98% to 1.1% (ICER<0)
- Next challenges:
  - Build evidence on the effectiveness of the PRP on longer period than 1 year and on its ability to delay TKR.

PRP Conclusions

- Major frontier in orthopaedic surgery and sports medicine will be lead by molecular biology and our ability to utilize these techniques clinically.
- Think as an adjuvant “Ideal cocktail”... GS/CS HA + PRP+ MSC+ Estradiol+ AF???
- Our present understanding of and maximizing the desired effect on the native tissue is at it’s infancy.. Good steps so far!
- Basic and clinical science is essential to discover the complexities of optimal regeneration
- Economics and social impact
- Need to be precise in not overstating the impact!..it is the TRIAD

THANK YOU
Cost-effectiveness and willingness to pay for an innovative regenerative therapy: The Platelet-Rich-Plasma for the intra-articular treatment of the knee Osteoarthritis

Salvatore Russo1, Stefano Landi1,2
1Dipartimento di Management, Università Cà Foscari Venezia
2Dipartimento di Economia, Università di Genova

Outline

Background
Objective
Therapies
Methods
Data Collection
Results
Conclusions and future work

Osteoarthritis (OA)

OA is a chronic and degenerative pathology affecting joints in particular hand, knee, hip and lower back resulting in joint inflammation with associated pain, stiffness and loss of movement.

- 10 % of world’s population (60yrs or more) is affected by OA (Woolf 2003)
- OA results to be the 11th out of 291 pathologies for Years Lived with Disability (YLDs) and 38th per disability adjusted life years DALYs (Murray et al., 2012, Cross M et al., 2014).
- In 2014, in Italy, OA resulted to be the 7th out of 283 diagnosis for Clinical Classifications Software (CCS) for number of hospital discharge (Italian Health Ministery hospital discharge data).
- OA is associated with older age and obesity. The increasing of these two population characteristics will lead to significant rises in prevalence.
- In western countries the number of total joint arthroplasty (TJR), which can be seen as the end stage of OA (knee and hip OA), is growing at a fast rate (Hiligsmann et al., 2013, Culliford et al, 2015).

Social and Economic Impact

The steady increasing, year after year, of surgery incidence will lead cost to grow (Piscitelli et al, 2004, Chen et al, 2012) for the foreseeable future (Hiligsmann et al., 2013, Culliford et al, 2015). In Italy 2001: 26,697 2007: 51,971 2014: 65,000

Source: Riap, Italian Arthroplasty Registry Project

Background

Symptomatic Prevalence (Pereira et al, 2011): :
- Knee OA 15.72 % (95% CI 15.15 – 16.29)
- Hip OA 8.21 % (95% CI 7.7 – 8.73)
- Hand OA 6.16 % (95% CI 5.71 – 6.62)

OA symptomatic prevalence in Italy (18-91yrs) (Salaffi, 2005):
- Knee OA: 5.39% (95% CI 3.41-7.99);
- Hip OA 1.61% (95% CI 1.39-1.87);
- Hand OA 1.95 (95% CI 1.22-2.48) (Salaffi, 2005)

Italians affected by knee OA: about 2,670,000 (Italy population, 2015, ISTAT)

ICER plane

Source: Riap, Italian Arthroplasty Registry Project
Results – 1 year scenario

ICER (Incremental Cost Effectiveness Ratio): €1,524.15/QALY

Probabilistic Sensitivity Analysis (PSA)

Cost Effectiveness Acceptability Curve – CEAC

WTP €30,000 – 82% iterations are cost-effective

Conclusions

- The i.a. PRP-based therapy, obtained with Regen Kit BCT-1, is a cost-effective therapy with respect to the i.a. HA in the 1 year scenario.
  - Future: build stronger evidence on the PRP effectiveness and standardize optimal “production” process.
  - “...cost-effective, if more evidence will confirm the data already collected...” Referee

Social and Economic Impact

OA burden of disease is associated to a high socioeconomic impact in terms of both direct health-related costs and indirect costs.

- OA has a significant impact on quality of life causing pain and decreased joint functionality leading to social life limitations and loss of work productivity.
- A recent systematic review concludes that the social cost of OA could be between 0.25% and 0.50% of a country’s GDP (Puig-Junoy et al., 2015).
- In Italy, annual total costs per patient have been estimated at €3,000 (€1,300 direct costs and €1,700 indirect costs) (Leardini et al., 2004).
- The cost for TKR is one of the main drivers of expenses for Health systems in case of OA disease (Chen et al., 2012).

The role of Intra-articular therapies

- Hyaluronic acid (HA) and platelet-rich-plasma (PRP) are two intra-articular (IA) infiltration therapies used between the pharmacological and the surgical phase, in order to delay or to avoid the surgery (Abbott et al., 2013; Altman et al., 2015; Ong et al. 2016).
- In the literature, both treatments have showed clinical effectiveness.
- HA is the standard of care for the IA therapy
- No economic analysis between the two therapies in the treatment of knee OA has previously been reported.

Conclusions

- Key points from the preliminary study on a longer period of time:
  - PRP can be cost-effective, also considering no social costs and no prosthesis revision were included in this study.
  - TKR incidence reduced from 1.98% to 1.1% (ICER<0)
  - Future challenges:
    - Building evidence on the effectiveness of the PRP on longer periods than 1 year and on its ability to delay TKR.
    - Ability to delay TKR will make PRP cost-saving for national health systems:
      - Increase patient quality of life
      - Increase NHS Willingness to pay for the therapy
    - Build a more accurate model to account for effectiveness and costs on the long period with several health states (starting from i.a. therapies to the prosthesis revision)
Objective

The aim of this study is to perform cost-effectiveness analysis of intra-articular injections of Platelet-Rich Plasma versus Hyaluronic acid in the treatment knee osteoarthritis.

Perspective: National Health System (direct costs)
Country: Italy
Time horizon: 1 and 5 years.

Therapies – Hyaluronic acid

Hyaluronic acid (HA) is an important visco-elastic component of the synovial fluid present inside the joints with lubricant and cushioning properties.

In joints affected by osteoarthritis the concentration of hyaluronic acid is decreased, and injections of hyaluronic acid into joints are therefore used to treat osteoarthritis.

Several clinical studies show the HA efficacy in knee OA treatment (Conrozier et al., 2009, Navarro et al., 2011, Altman et al. 2011, Pal et al., 2014)

HA, compared to corticosteroids infiltrations, has a longer lasting effect (Bruyere et al, 2014, Askari et al., 2016).

Considering direct cost and costs bound to potential side effects, it has been showed the cost-effectiveness of HA compared to oral NSAIDs, physical therapy and assistive device (Hatoum et al., 2014).

Therapies – Platelet Rich Plasma

The PRP treatment efficacy is showed in several studies (Kon et al., 2010, Sampson et al., 2010, Kon et al., 2011, Saad Setta et al., 2011, Filardo et al., 2011, Waeng-Saegusa et al., 2011, Sanchez et al., 2012).

Several studies comparing HA and PRP effectiveness have been found. In knee OA treatment, PRP has major effectiveness than HA (Kon et al,2011, Filardo et al, 2011, Sanchez et al., 2012, Spakova et al 2012, Cerza et al., 2012, Raissadat et al., 2015).

The results of several meta-analyses confirm the major effectiveness of PRP (Khoshbin et al., 2013, Chang et al. 2014, Ludy et al, 2014, Campbell et al., 2015).

The particular method to produce PRP needs a medical device and a longer time consuming process, leading the therapy to be more costly than HA.

Better effectiveness and higher costs
The medical device taken as reference for this work is the Regen kit BCT-1©, manufactured by Regenlab (CH), is a simplified, sterile kit for PRP preparation that easily permits to separate plasma and platelets from other blood components obtaining a PRP ready to use.

Methods

- Decision tree models have been developed to assess costs and clinical benefits of the two treatments.
- The outcomes of the model will be expressed in terms of quality adjusted life years (QALYs).
- Results will be reported in terms of Incremental Cost Effectiveness Ratio (ICER).
- Deterministic and probabilistic sensitivity analyses will be carried out in order to test the robustness of the results.

Decision Tree Model

Two lifetime scenarios:
- 1 years cost-effectiveness analysis PRP vs HA
  - Clinical evidences, 1 year follow up
- 5 years cost-effectiveness analysis PRP vs HA
  - To take account of OA final stage, Total knee replacement - TKR.
  - No clinical evidences, need assumptions
  - Scenario analysis

Decision Tree Model

- Do we use PRP or HA?
- PRP: Effective (p=0.80)
- Not effective (p=0.2)
- HA: Effective (p=0.80)
- Not effective (p=0.2)
Methods

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Methods

Illness specific scales are very sensitive to changes in patients’ conditions and they are accurate to evaluate improvement related to a certain treatment.

The general health status profiles (Health related quality of life, HRQoL) are less sensitive, but allow to compare results also out of the context of a certain pathology and with the willingness to pay (WTP) for a therapy.

WOMAC scale (Western Ontario & Mc Master University Arthritis Index) have been mapped in to HRQoL through a regression model estimated by Wailoo et al, 2014

Methods

- Decision tree models have been developed to assess costs and clinical benefits of the two treatments.
- The outcomes of the model will be expressed in terms of quality adjusted life years (QALYs).
- Results will be reported in terms of Incremental Cost Effectiveness Ratio (ICER).
- Deterministic and probabilistic sensitivity analyses have been carried out.

ICER

\[
\text{ICER} = \frac{(C_1 - C_0)}{(E_1 - E_0)}
\]

- \(C_0\) = Total Cost of HA strategy
- \(C_1\) = Total Cost of PRP strategy
- \(E_0\) = Effectiveness of HA strategy
- \(E_1\) = Effectiveness of PRP strategy

ICER & Willingness to pay

The ICER represents the cost for a QALY, that is one year of life with perfect health.

This value has to be compared with the Willingness to pay for a QALY.

Several thresholds exist depending on the country and on the type of disease.

- NICE (National Institute of Care and Excellence) \(\rightarrow\) £30,000
- Italy \(\rightarrow\) €17,000 – 30,000 (Fattore et al, 2009, Mennini et al, 2009)

In this work it has been used a conservative threshold at €10,000

Methods
Methods

Deterministic and probabilistic sensitivity analyses have been carried out to test the robustness of the tree models and take into account:

- Model uncertainty, it is a simplification of the reality
- Parameter uncertainty, in the estimation of costs and effectiveness
- Heterogeneity, individual variability between patients

Outline

- Background
- Objective
- Therapies
- Methods
  - Data Collection
  - Results
  - Conclusions and future work

Data - Utility

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Base case (E)</th>
<th>Range</th>
<th>Clients</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>HA Therapy</td>
<td>0.035</td>
<td>0.030-0.05</td>
<td>Uniforms</td>
<td>Ramous et al., 2015</td>
</tr>
<tr>
<td>PRP Therapy</td>
<td>0.080</td>
<td>0.070-0.080</td>
<td>Uniforms</td>
<td>Ramous et al., 2015</td>
</tr>
<tr>
<td>Therapies not effective</td>
<td>0.040</td>
<td>0.030-0.050</td>
<td>Uniforms</td>
<td>Ramous et al., 2015</td>
</tr>
<tr>
<td>TEB</td>
<td>0.02</td>
<td>0.02-0.03</td>
<td>Beta</td>
<td>Navarro &amp; Ivens, 2000</td>
</tr>
</tbody>
</table>

Data - Costs

Only direct medical costs have been included.

PRP is more costly because:

- Medical device
- Time consuming process

The HA treatment needs only the IA injection time, while the PRP treatment takes 2 minutes for the plasma withdrawal from the patient, around 7 minutes for the centrifugation and the other operations previously cited and finally 2 minutes for the injection that are in common for both therapies.
**Results – 1 year scenario**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Cost</th>
<th>Incremental Cost</th>
<th>Effectiveness(QALYs)</th>
<th>Incremental effectiveness</th>
<th>ICER (€/qaly)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRP</td>
<td>154.64€</td>
<td>82.62€</td>
<td>0.7002</td>
<td>0.0472</td>
<td>€1,524.15/qaly</td>
</tr>
<tr>
<td>HA</td>
<td>82.62€</td>
<td></td>
<td>0.6053</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The average cost per QALY is respectively €127.1 for the HA and €220.8 for the PRP. The incremental effectiveness of the PRP is 0.0472 QALY with an incremental cost of 71.94€.

**Deterministic Sensitivity Analysis (DSA)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Therapy Cost</th>
<th>Incremental Cost</th>
<th>Effectiveness</th>
<th>Incremental Effectiveness</th>
<th>ICER (€/qaly)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>154.64€</td>
<td>82.62€</td>
<td>0.7002</td>
<td>0.0472</td>
<td>€1,524.15/qaly</td>
</tr>
<tr>
<td>High</td>
<td>154.64€</td>
<td>82.62€</td>
<td>0.6053</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Probabilistic Sensitivity Analysis (PSA)**

It was carried out a probabilistic sensitivity analysis through a Monte Carlo simulation (considering 10,000 iterations) making all the parameters and variables of the model variate according to the assigned distribution. Establishing a conservative Willingness To Pay of €10,000 per QALY, the PRP is cost-effective in the 78.6% of the iterations.

**Tornado analysis (ICER)**

**Decision Tree Model – Five year’s scenario**

TKR costs is the main driver of OA direct health cost for NHS

Reducing the steady increase of surgical interventions can help to lower the social and economic burden on NHS.

In literature there are early studies showing a positive relation between IA therapies, as HA, and the delay of the TKR surgery (Altman 2015)

There are no studies showing the PRP ability to delay the TKR yet.

Since PRP appears to be more effective and cost-effective, with respect to HA, we may assume that it can delay the surgery at a higher rate.

Threshold analysis has been made in order to point out the outcomes needed to make the therapy cost-saving.

**Decision Tree Model – Five year’s scenario**

Using the prevalence in Italy of knee OA (Salaffi 2005) and the number of TKR in 2013 (RIAP) we calculate the current incidence in OA affected population (1.98%).

For the base case scenario we fixed the PRP therapy incidence reduction at 1.2%

The Geometric distribution has been used to compute the aggregate probabilities to undergo TKR.

\[
P(T \leq k) = 1 - P(T > k + 1) = 1 - q^k
\]

In this way we can estimate the probability to undergo TKR within a certain period of time.
**Results – 5 years**

The incremental effectiveness of the PRP is 0.21 QALY with an incremental cost of 34€.

**ICER** (Incremental Cost Effectiveness Ratio): €162/QALY

Considering PRP does not change TKR incidence: ICER €1,285/QALY

Cost of TKR incidence reduced from 1.98% to 1.1% (ICER<0)

**1-saving threshold:**
- TKR direct and indirect costs were up to €10,000
- Probability for a patient to be responders (0.9 instead of 0.8)

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**Decision Tree Model – Five year’s scenario**

It was carried out a PSA through a Monte Carlo simulation (considering 10,000 iterations).

With Willingness To Pay of €1,000 per QALY, the PRP is cost-effective in the 82% of the iterations.

35% of the iterations are cost-saving (vs 5% of 1 year model)

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**Results – 5 years**

**Decision Tree Model – Five year’s scenario**

**Outline**

- Background
- Objective
- Therapies
- Methods
- Data Collection
- Results
- Conclusions and future work

**Thank you for your attention!**
References


