RÉPUBLIQUE FRANÇAISE
Liberté
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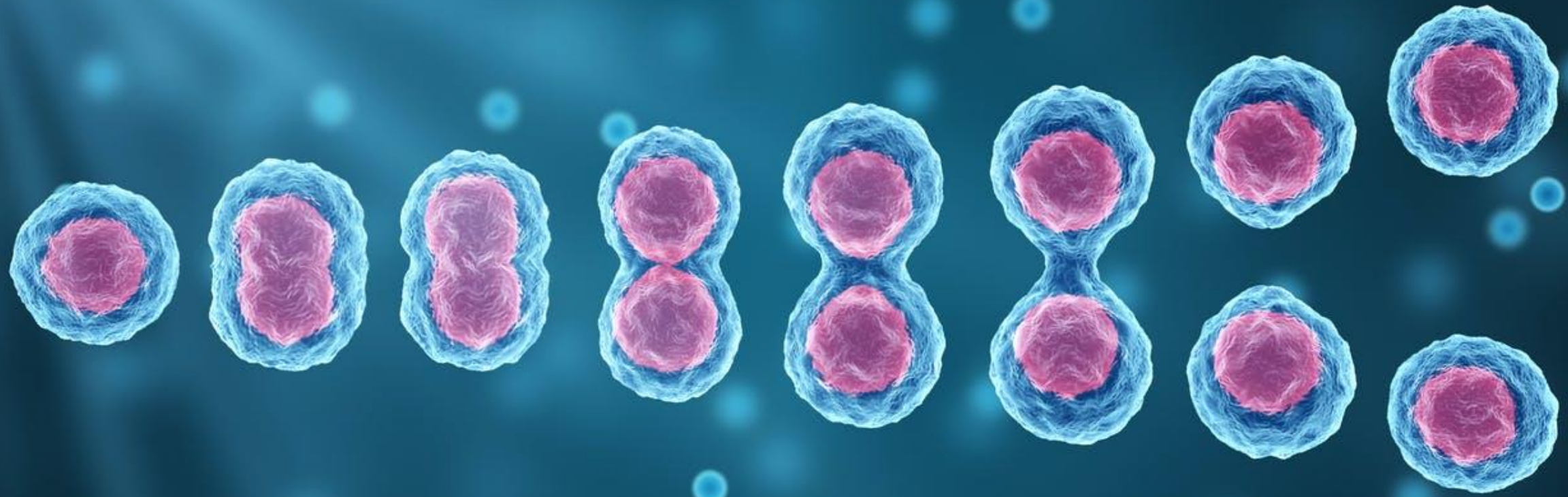
Oniris
ÉCOLE NATIONALE
VÉTÉRINAIRE, AGROALIMENTAIRE ET DE L'ALIMENTATION

CAP douleur
CHANGE ANIMAL PAIN

WEBINAIRE
CELLULES SOUCHES ET ARTHROSE CANINE



24 AVRIL 2023

Olivier Gauthier, Pr. Unité de chirurgie, Oniris, Nantes
Thierry Poitte DMV DIU Douleur CES Traumatologie et Chirurgie Ostéo-Articulaire île de Ré

Traiter l'arthrose par injection de cellules souches ?

- 20% de la population canine = 1ère maladie orthopédique du chien
- ARTHROSE =affection articulaire dégénérative (Osteoarthritis)
  - inflammation non suppurée de l'articulation
  - lésions précoces du cartilage articulaire
  - remodelage de l'os sous-chondral
  - proliférations ostéophytiques aux limites des surfaces articulaires
  - modifications des tissus mous péri-articulaires

- Syndrome complexe: interactions de facteurs biomécaniques, biochimiques, inflammatoires = réaction immunologique

- Etiopathogénie partiellement élucidée :
  - arthrose mécanique (acquise : trauma direct, surutilisation) versus
  - arthrose conformationnelle (dysplasie, OCD …) versus
  - arthrose à médiation immune (« Ostéoarthrite », polyarthrite, maladie du LCCr ?)

Traiter l'arthrose par injection de cellules souches ?

Définition OARSI 2015 (Osteoarthritis Research Society International)

« L'arthrose est un trouble des articulations mobiles caractérisé par un stress cellulaire et une dégradation de la matrice extracellulaire initiés par des micro et macro-lésions qui activent des réponses de réparation inadaptées, notamment des **voies pro-inflammatoires de l'immunité innée**. Elle se manifeste d'abord par un **dérèglement moléculaire** (métabolisme anormal des tissus articulaires) suivi de **dérèglements anatomiques** et/ou physiologiques (caractérisés par la dégradation du cartilage, le remodelage osseux, la formation d'ostéophytes, l'inflammation articulaire et la perte de la fonction articulaire normale), qui peuvent aboutir à une **maladie**. »

Comparaison entre une articulation saine et une articulation arthrosique

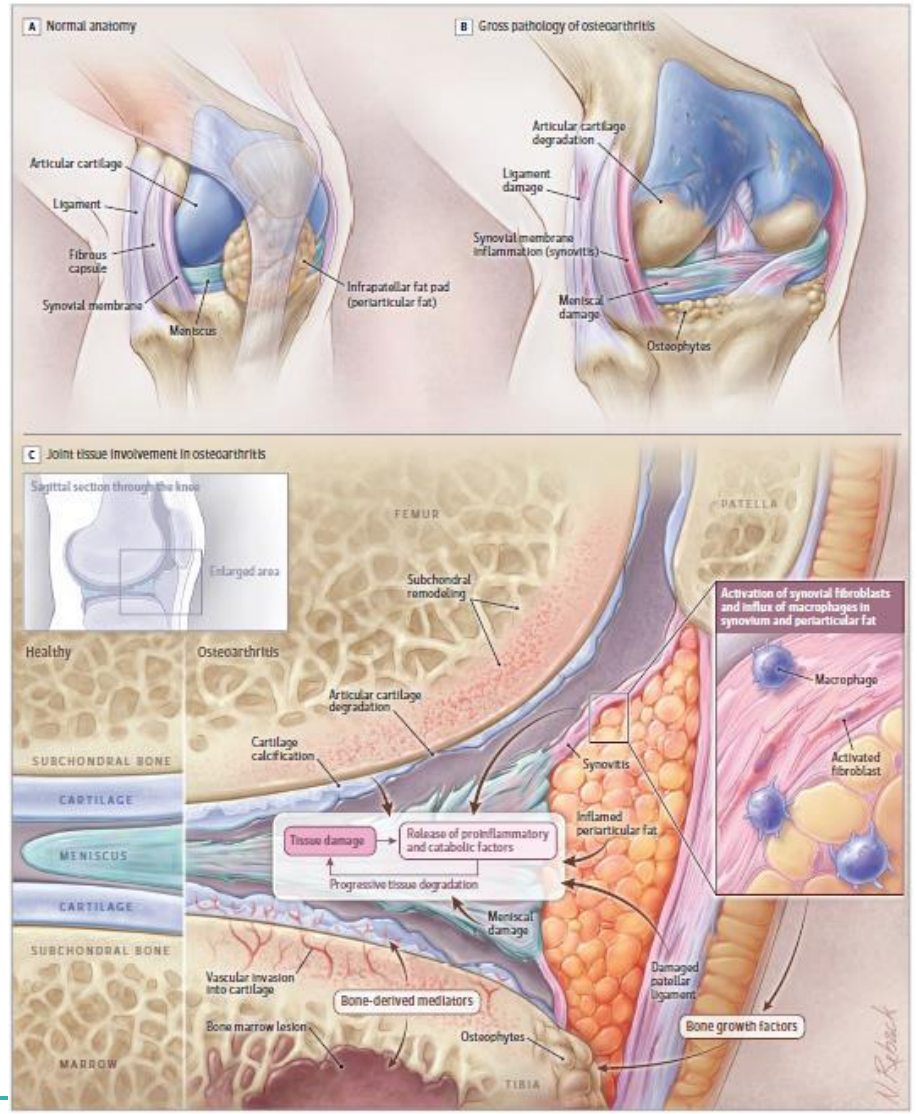
L'arthrose se caractérise par un ensemble d'altérations progressives:

- lésions du cartilage
- lésions ligamentaires et méniscales
- remodelage osseux sous-chondral
- formation d'ostéophytes
- inflammation de la membrane synoviale

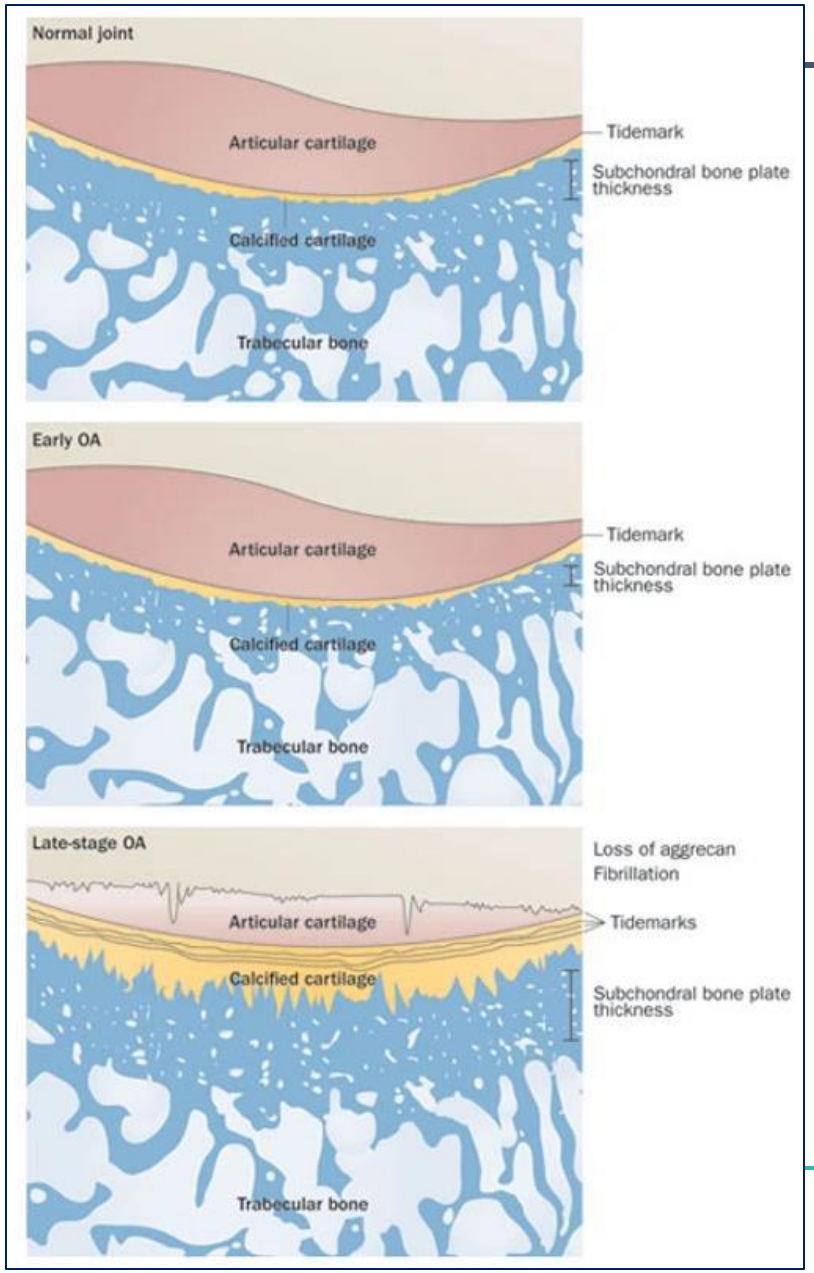
⇒ Production de nombreux facteurs pro-inflammatoires et d'enzymes

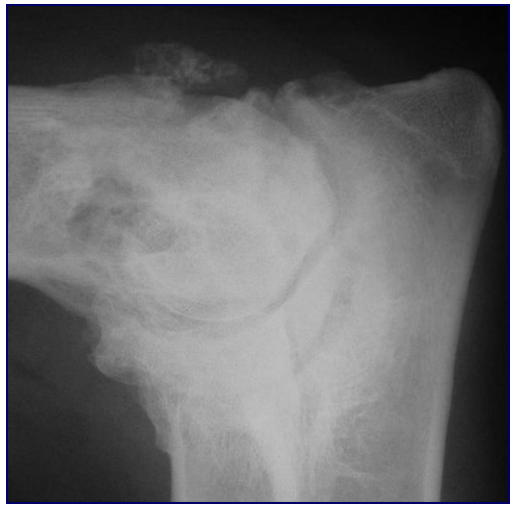
⇒ Dégradation de la matrice extracellulaire

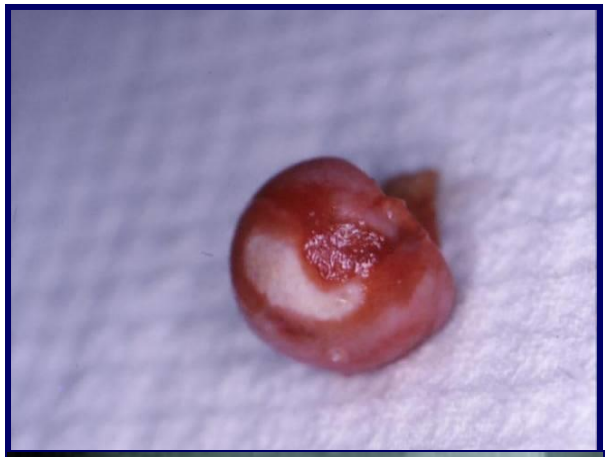
⇒ Destruction de l'articulation

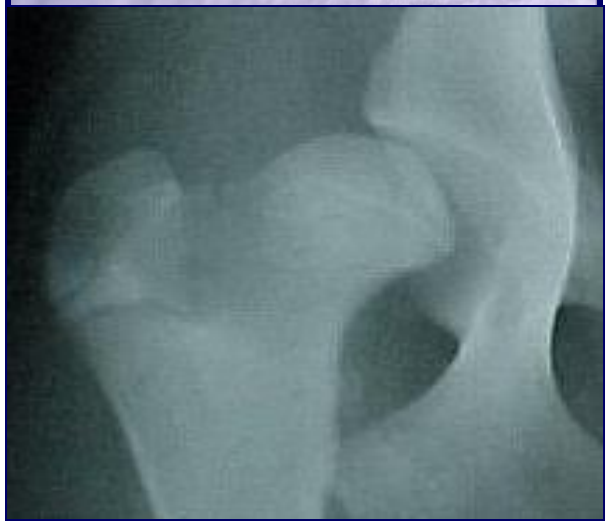


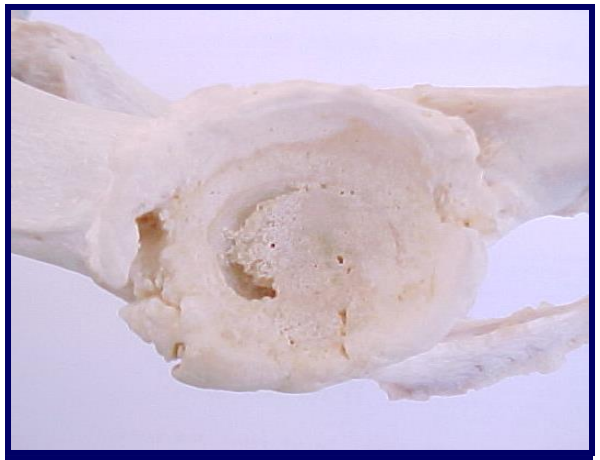
Pourquoi l'arthrose est-elle douloureuse?

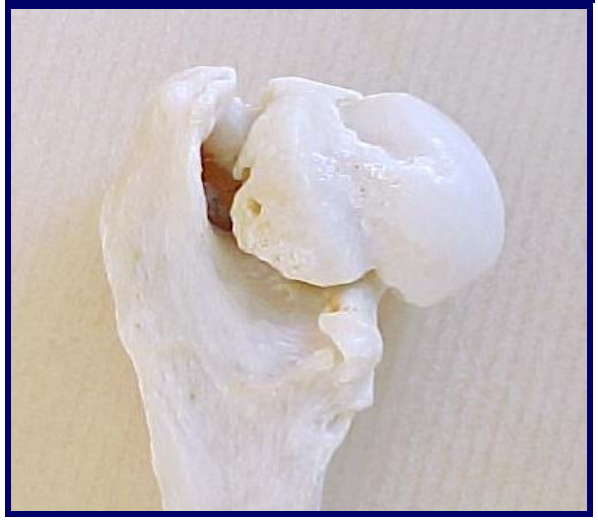






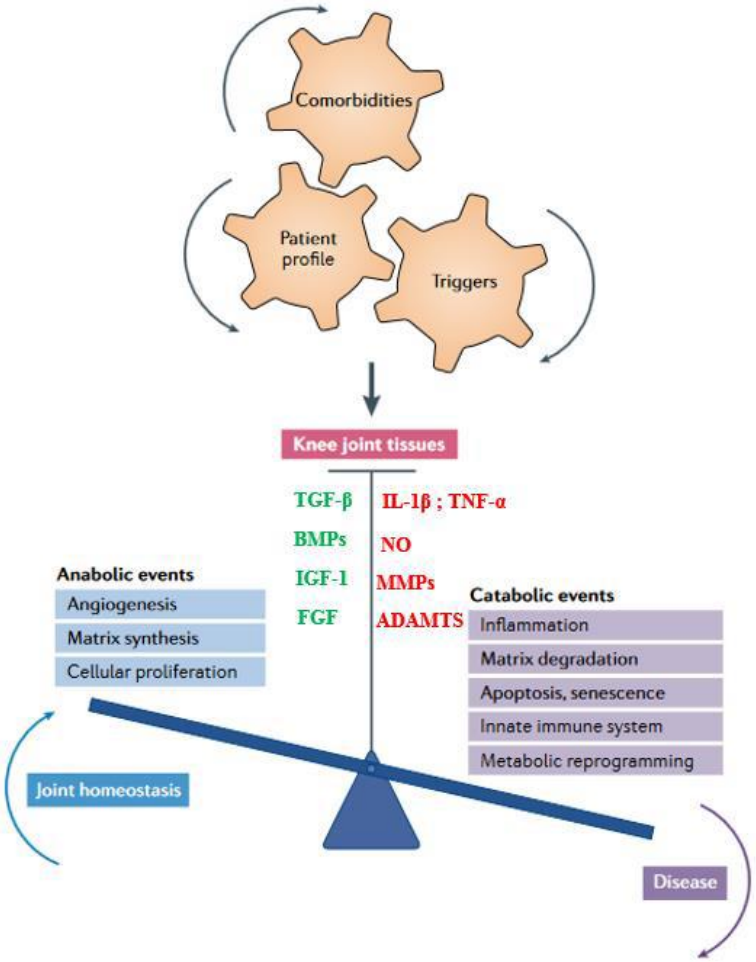


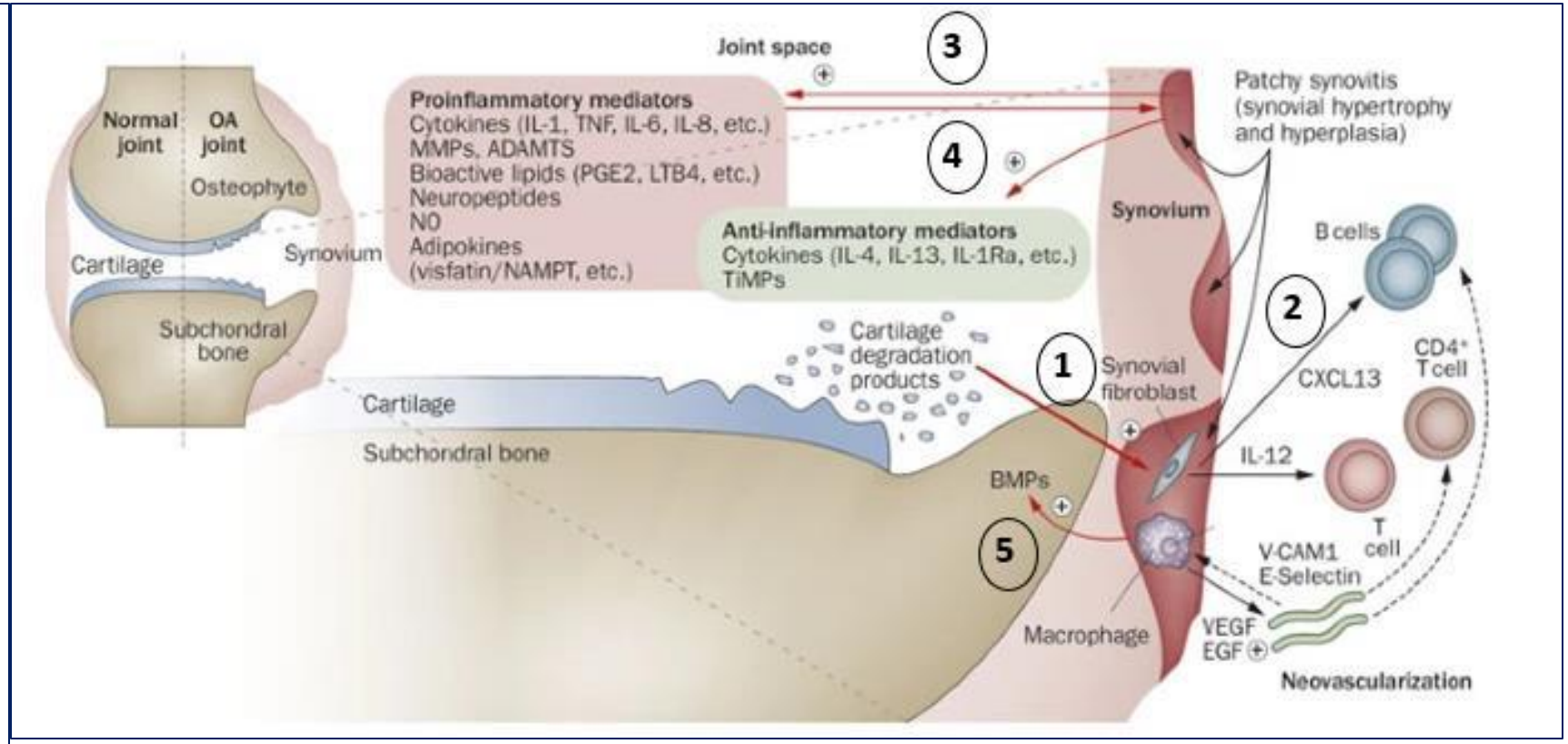




⇒ **Remaniements sous-chondraux**

Pourquoi l'arthrose est-elle douloureuse?





⇒ **Inflammation globale (membrane synoviale)**

Objectif thérapeutique : une approche multimodale

- Réduire l'inflammation
- Soulager la douleur
- Améliorer la fonction
- Limiter la progression des phénomènes dégénératifs
- Favoriser les processus de réparation

- **Consensus OARSI, AAOS (American Academy of Orthopédic Surgeons), ACR (American College of Rheumatology), EULAR (European League Against Rheumatism)**

⇒ **Prise en charge par une combinaison de thérapies pharmocologiques et non-pharmacologiques**

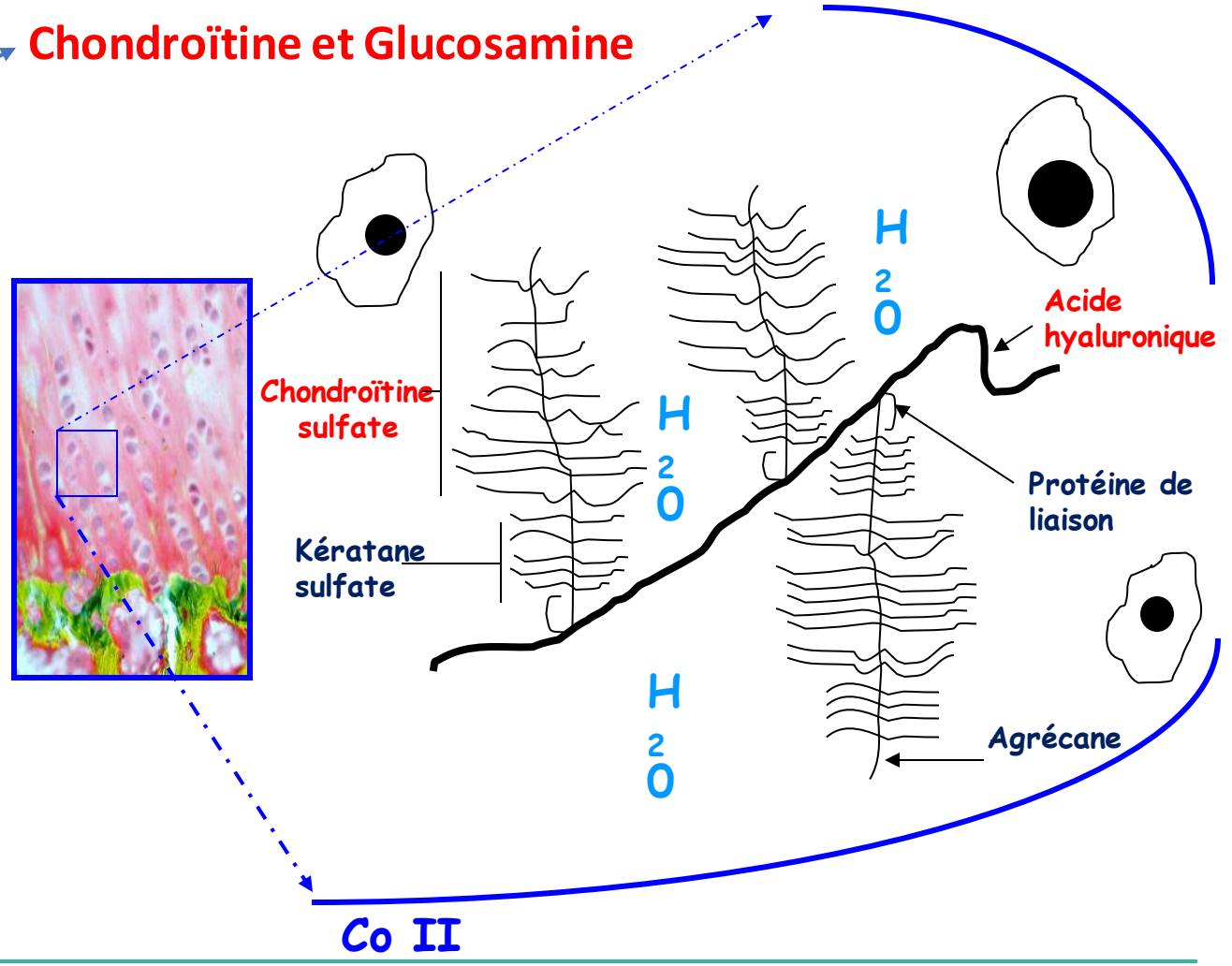
Objectif thérapeutique : une approche multimodale

❑ Médical

- ➢ **AINS**
- ➢ **Chondroprotecteurs**
- ➢ **Acide hyaluronique (viscosupplémentation),**

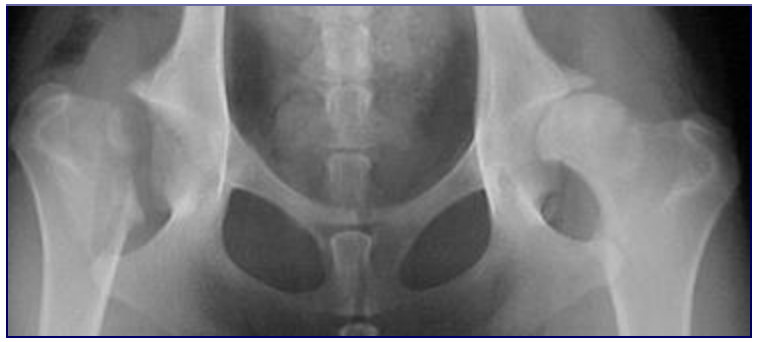
voire Cox2 inhibiteurs en IA …

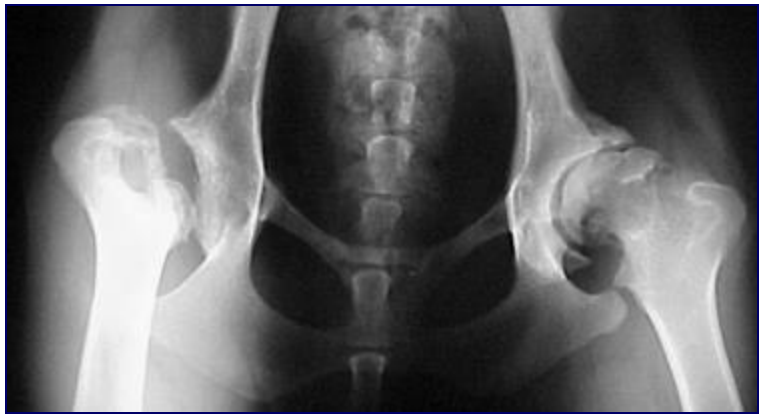
- ➢ **GAG et pentosane polysulfatés**
- ➢ **Acides gras polyinsaturés oméga 3**
- ➢ **Insaponifiables de soja et d'avocat**
- ➢ **Homéopathie**
- ➢ **Tétracyclines**

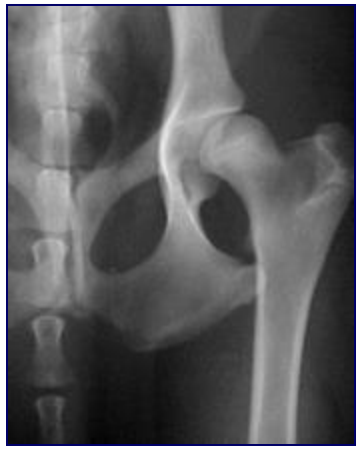


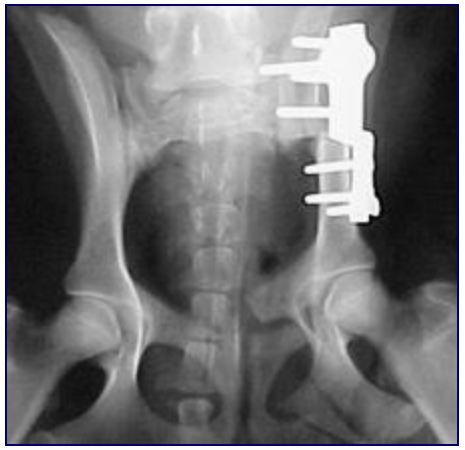
Objectif thérapeutique : une approche multimodale

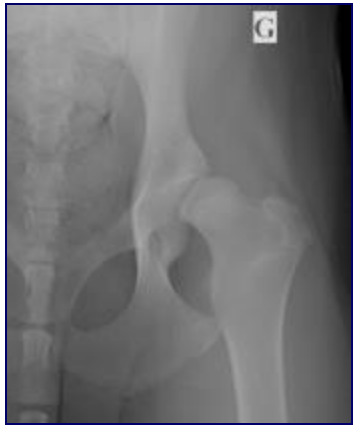
❑ Chirurgical

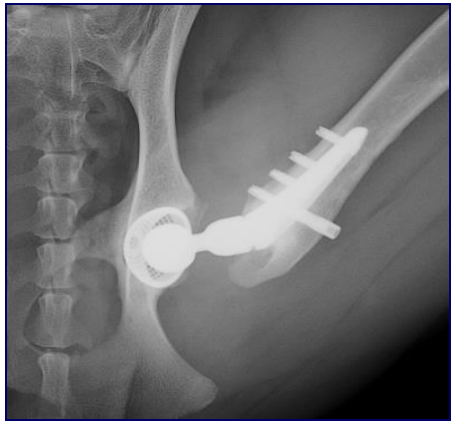


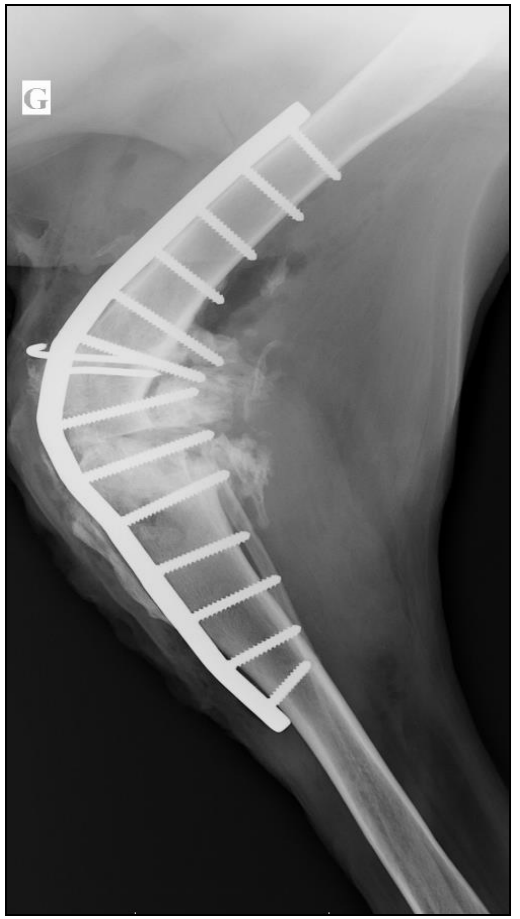












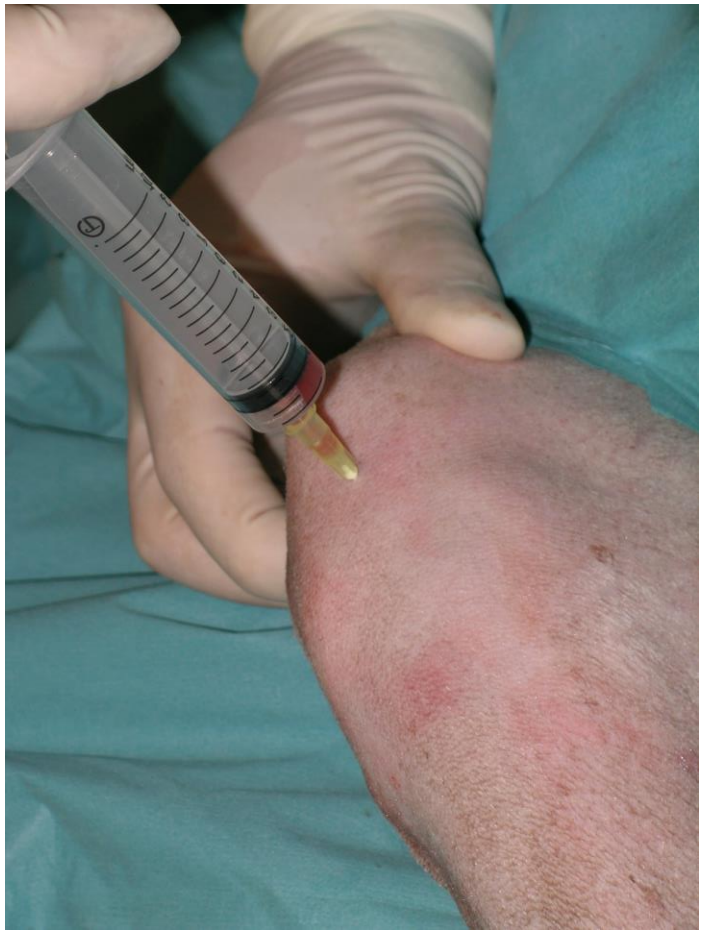
Objectif thérapeutique : une approche multimodale

En 2010 :

- (presque) Rien sur les injections intra articulaires
- Rien sur les PRP
- Rien sur la thérapie cellulaire et la médecine régénératrice (Ç souches)

Traitements intra articulaires

- Principes généraux
  - Cibler la ou les articulations douloureuses
  - Thérapeutique locale
  - Eviter ou retarder le recours aux traitements systémiques et leurs effets indésirables



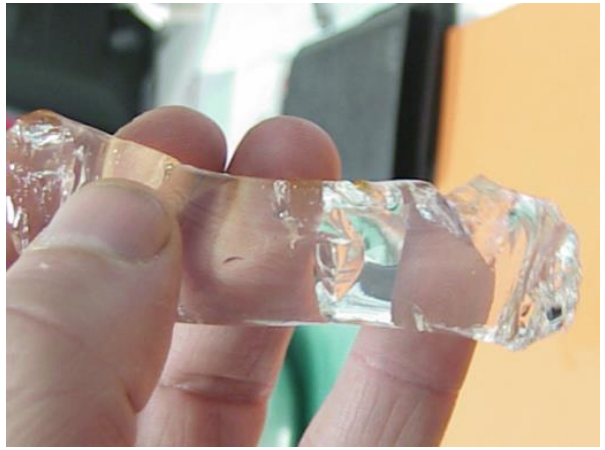
  - Geste technique «anodin» = arthrocenthèse ….

Mais non dénué de complications potentielles: arthrite septique …

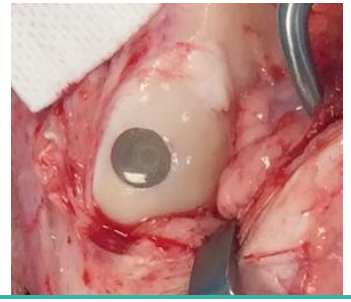
Quels traitements intra articulaires ?

- Molécules à visée de « viscosupplémentation » : acide hyaluronique

- Molécules et principes actifs à visée immunomodulatrice et régénératrice :
  - Plasma riche en plaquettes
  - Ingénierie tissulaire
  - Cellules souches



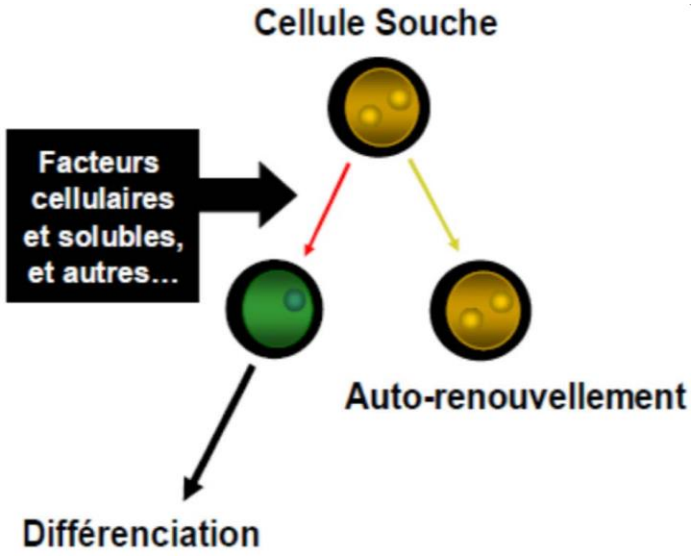
- Implants prothétiques

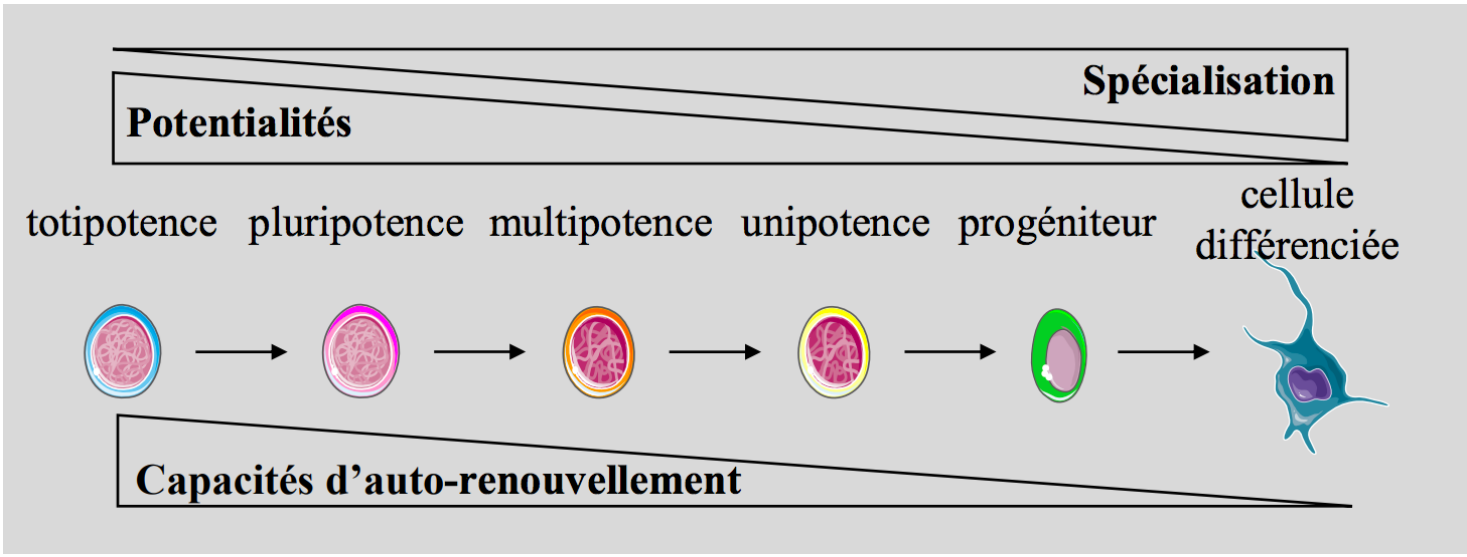


Propriétés des cellules souches

DÉFINITIONS

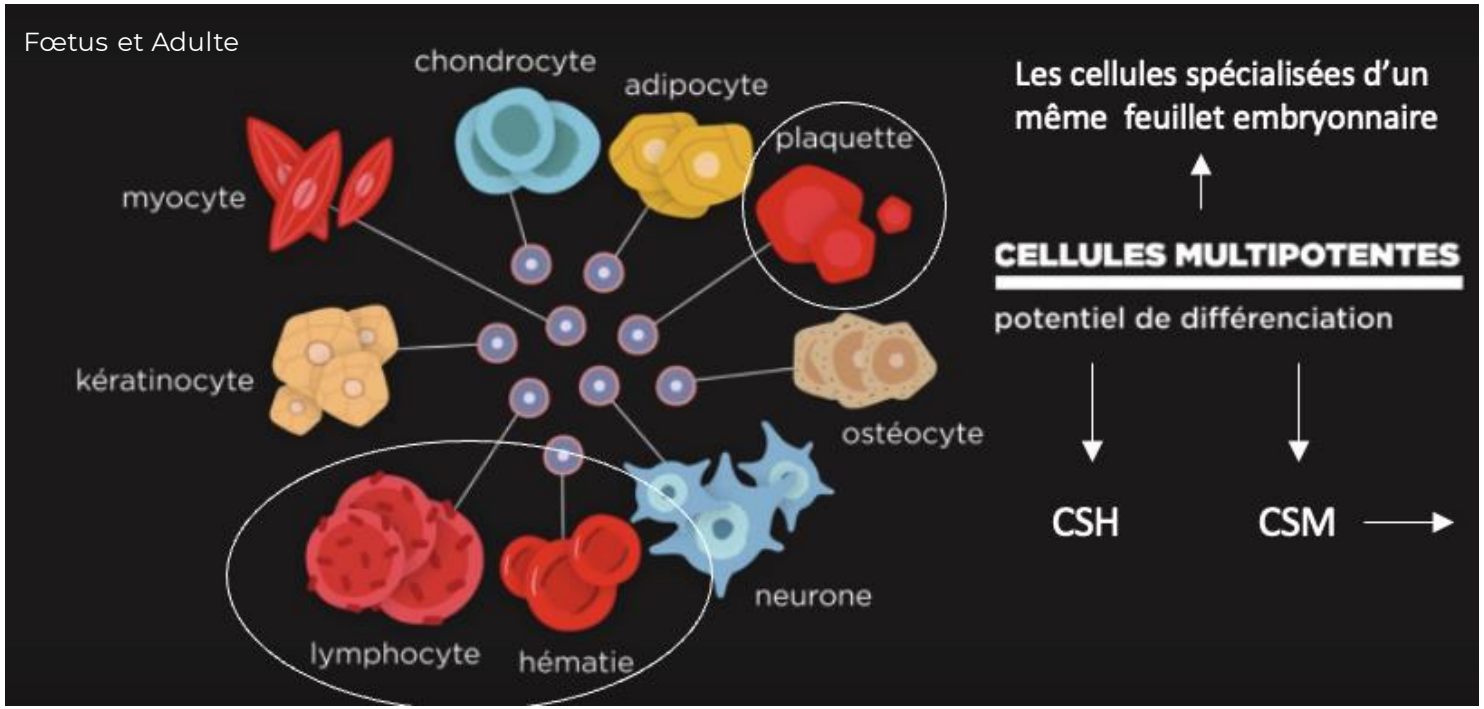
= Cellule souche = cellule indifférenciée:
1° Potentiel de différenciation *en au moins un type cellulaire.*
2° Auto-renouvellement *en maintenant un état indifférencié*

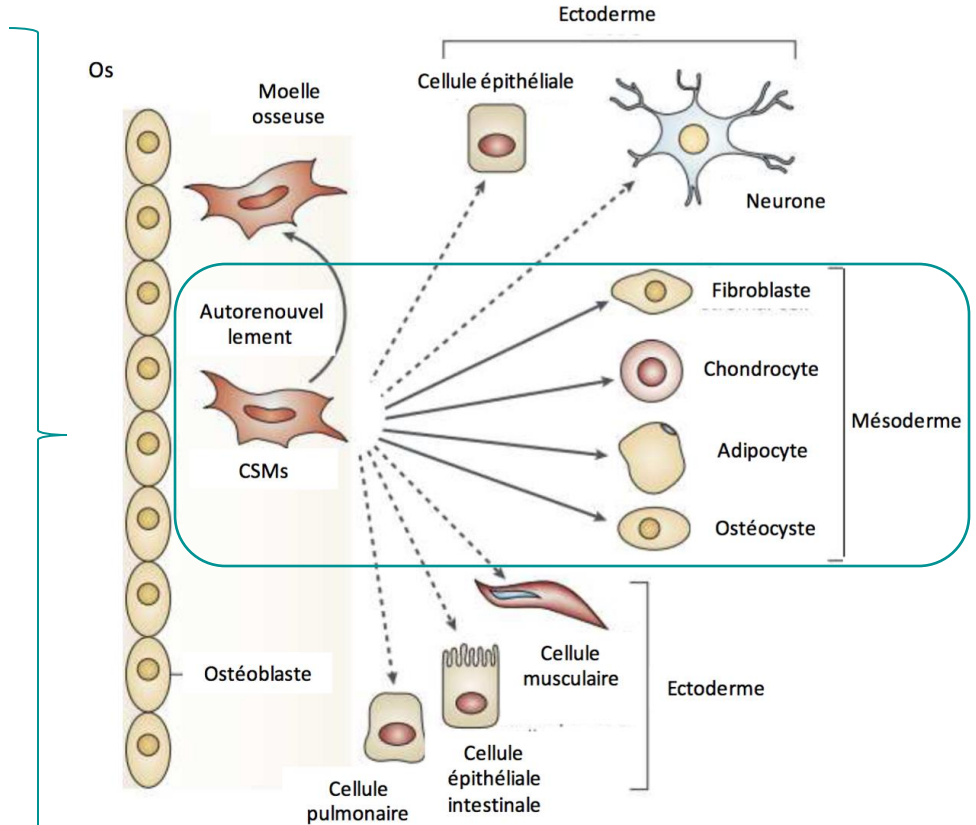




Propriétés des cellules souches mésenchymateuses

CAPACITÉS DE DIFFÉRENCIATION

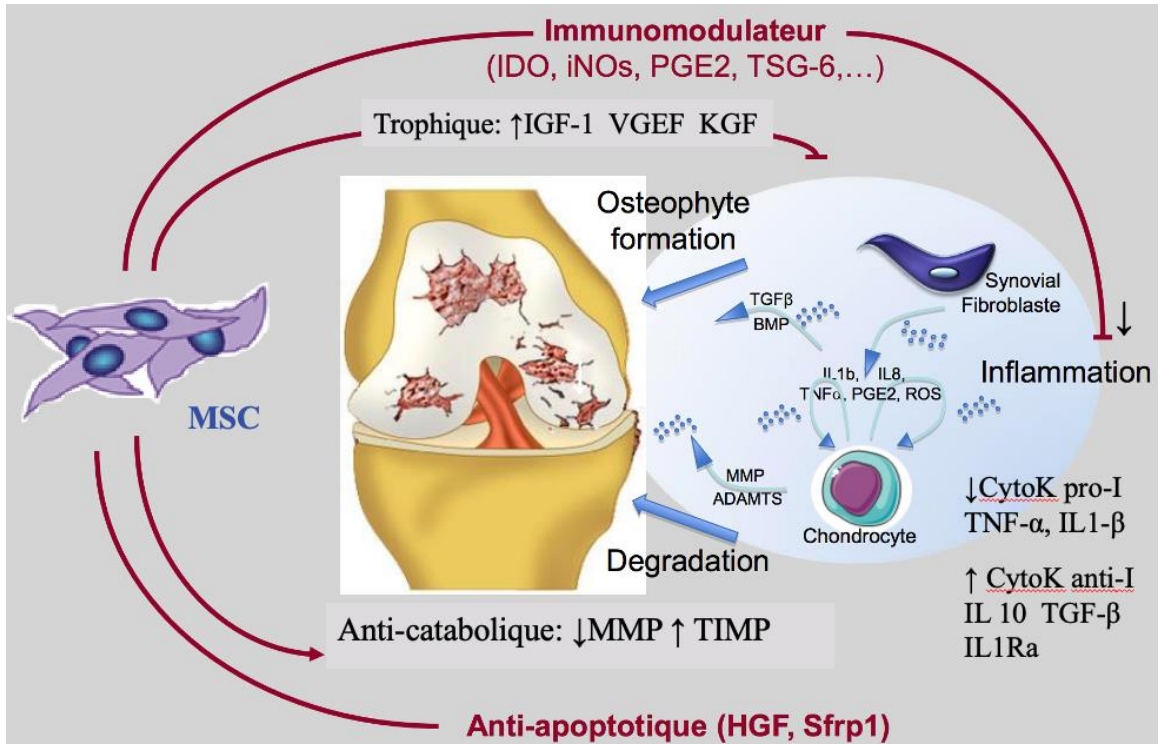




Les CSMs se différencient classiquement en cellules mésodermiques: ostéoblastes, chondroblastes, adipocytes ou fibroblastes

Propriétés des cellules souches mésenchymateuses

PHARMACODYNAMIE



Activité paracrine des CSM

- **Effet anti-inflammatoire:**
  sécrétion de cytokines anti-inflammatoires
  IL1Ra, IL10, TGF-β
  ciblage ☞ membrane synoviale

- **Effet anti-catabolique**
  ↓ métalloprotéases (MMP)
  ciblage ☞ cartilage ;

- **Effet immunomodulateur**
  expression de PGE2 - TGF-β1 (facteur de croissance transformant)
  expression de IDO (facteurs immunosuppresseurs)
  ☞ équilibre cytokinique local
  ↓ cytokines pro-inflammatoires (TNF-α, IL1-β)

- **Effet trophique**
  IGF-1 Insuline Growth Factor ☞ chondrogenèse
  VEGF Vascular Endothelial Growth Factor ☞ angiogenèse
  KGF Keratinocyte Growth Factor ☞ ↓ fibrose

Wang J, Liao L, Tan J. Mesenchymal-stem-cell-based experimental and clinical trials: current status and open questions. Expert Opin Biol Ther 2011;11:893–909.

Propriétés des cellules souches mésenchymateuses

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Les CSM sont des cellules de signalisation secrétant:

1° Facteurs immunomodulateurs
- Régulation cytokines

2° Facteurs trophiques
- IGF-1 Insuline Growth Factor
  Chondrogenèse
- VGEF Vascular Endothelial Growth Factor
  Angiogenèse
- KGF Keratinocyte Growth Factor
  ↓ Fibrose

Stimulation cellules souches locales
Chondrogenèse endogène

STEM CELLS TRANSLATIONAL MEDICINE

PERSPECTIVES

Mesenchymal Stem Cells: Time to Change the Name!

ARNOLD I. CAPLAN

Skeletal Research Center, Department of Biology, Case Western Reserve University, Cleveland, Ohio, USA

Key Words. Medicinal signaling cells • Mesenchymal stem cells • MSCs • Regenerative medicine

SUMMARY

Mesenchymal stem cells (MSCs) were officially named more than 25 years ago to represent a class of cells from human and mammalian bone marrow and periosteum that could be isolated and expanded in culture while maintaining their in vitro capacity to be induced to form a variety of mesodermal phenotypes and tissues. The in vitro capacity to form bone, cartilage, fat, etc., became an assay for identifying this class of multipotent cells and around which several companies were formed in the 1990s to medically exploit the regenerative capabilities of MSCs. Today, there are hundreds of clinics and hundreds of clinical trials using human MSCs with very few, if any, focusing on the in vitro multipotential capacities of these cells. Unfortunately, the fact that MSCs are called "stem cells" is being used to infer that patients will receive direct medical benefit, because they imagine that these cells will differentiate into regenerating tissue-producing cells. Such a stem cell treatment will presumably cure the patient of their medically relevant difficulties ranging from osteoarthritic (bone-on-bone) knees to various neurological maladies including dementia. I now urge that we change the name of MSCs to Medicinal Signaling Cells to more accurately reflect the fact that these cells home in on sites of injury or disease and secrete bioactive factors that are immunomodulatory and trophic (regenerative) meaning that these cells make therapeutic drugs in situ that are medicinal. It is, indeed, the patient's own site-specific and tissue-specific resident stem cells that construct the new tissue as stimulated by the bioactive factors secreted by the exogenously supplied MSCs. STEM CELLS TRANSLATIONAL MEDICINE *2017;6:1445–1451*

INTRODUCTION

Mesenchymal stem cells (MSCs) were officially named more than 25 years ago [1] to represent a class of cells from human [2] and mammalian bone marrow and periosteum [3] that could be isolated and expanded in culture while maintaining their in vitro capacity to be induced to form a variety of mesodermal phenotypes and tissues (Fig. 1, The Mesengenic Process). The in vitro capacity to form bone, cartilage, fat, etc., became an assay for identifying this class of multipotent cells [9] and around which several companies (including Osiris Therapeutics, which my colleagues and I started,) were formed in the 1990s to medically exploit the regenerative capabilities of MSCs. Initially, the driving concept that a multipotent progenitor or "stem cell" existed in adult marrow was not only challenged, but was actively disregarded, especially by the orthopedic industry. Fast-forward to today and there are hundreds of clinics [10] and hundreds of clinical trials [11] using human MSCs (hMSCs) with very few, if any, focusing on the in vitro multipotential capacities of these cells.

Unfortunately, the fact that MSCs are called "stem cells" is being used to infer that patients will receive direct medical benefit, because they imagine that these cells will differentiate into the regenerating tissue-producing cells (i.e., these "stem cells" will be incorporated into and these differentiated cells will fabricate the diseased or missing tissue). Such a stem cell treatment will presumably cure the patient of their medically relevant difficulties ranging from osteoarthritic (bone-on-bone) knees to various neurological maladies, including dementia. I long ago urged, in print, that we change the name of MSCs to Medicinal Signaling Cells [12] to more accurately reflect the fact that these cells home in on sites of injury or disease and secrete bioactive factors [13] that are immunomodulatory and trophic [14] (regenerative), meaning that these cells make therapeutic drugs [15] that are medicinal. It is, indeed, the patient's own site-specific and tissue-specific resident stem cells that construct the new tissue as stimulated by the bioactive factors secreted by the exogenously supplied MSCs [16, 17].

HISTORY OF MSCs FROM A CAPLAN PERSPECTIVE

In the early 1970s into the 1980s, my colleagues and I published a number of papers based on the culturing of stage 24, embryonic chick limb bud mesodermal cells (ECLBMCs) that were observed to differentiate into cartilage, muscle, and bone under certain culture conditions [18–22]. These in vitro studies were correlated with a variety of in vivo studies that focused on the cellular and molecular events associated with the formation of embryonic limb bone [23, 24], cartilage [25], and muscle [26] in which several very prominent dogmas-of-the-day were challenged. For example, the concept that "cartilage is replaced by bone" led to the implication that if one

Correspondence: Arnold I. Caplan, Ph.D., Skeletal Research Center, Department of Biology, Case Western Reserve University, 10600 Euclid Avenue, Cleveland, Ohio 44106, USA. Telephone: 216-368-3562; Fax: 216-368-4077; e-mail: arnold.caplan@case.edu.
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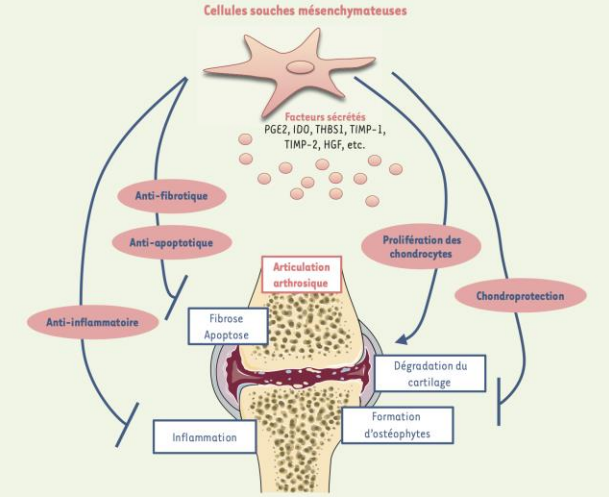
Propriétés des cellules souches mésenchymateuses

PHARMACODYNAMIE

DMOAD ?
DISEASE MODIFYING OSTEOARTHRITIS DRUGS

= Traitements + efficaces et disruptifs ?
Ambition:
Agir à la fois sur la douleur
et sur les changements structurels,
afin de prévenir et/ou de guérir l'arthrose.



Drug Design, Development and Therapy
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REVIEW

The Development of Disease-Modifying Therapies for Osteoarthritis (DMOADs): The Evidence to Date

Win Min Oo[1,2]
Christopher Little[3]
Vicky Duong[1]
David J Hunter[1]

[1]Rheumatology Department, Royal North Shore Hospital, and Institute of Bone and Joint Research, Kolling Institute, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia; [2]Department of Physical Medicine and Rehabilitation, Mandalay General Hospital, University of Medicine, Mandalay, Mandalay, Myanmar; [3]Raymond Purves Bone and Joint Research Laboratories, Institute of Bone and Joint Research, Kolling Institute, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia

Correspondence: David J Hunter
Rheumatology Department, Royal North Shore Hospital, and Institute of Bone and Joint Research, Kolling Institute, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia
Email david.hunter@sydney.edu.au

Abstract: Osteoarthritis (OA) is a complex heterogeneous articular disease with multiple joint tissue involvement of varying severity and no regulatory-agency-approved disease-modifying drugs (DMOADs). In this review, we discuss the reasons necessitating the development of DMOADs for OA management, the classifications of clinical phenotypes or molecular/mechanistic endotypes from the viewpoint of targeted drug discovery, and then summarize the efficacy and safety profile of a range of targeted drugs in Phase 2 and 3 clinical trials directed to cartilage-driven, bone-driven, and inflammation-driven endotypes. Finally, we briefly put forward the reasons for failures in OA clinical trials and possible steps to overcome these barriers.

Keywords: osteoarthritis, DMOADs, disease-modifying drugs, intra-articular therapy, phenotype, endotype

Why is the Development of Disease-Modifying Osteoarthritis Drugs (DMOADs) Required?

Disease Burden

Osteoarthritis (OA) is the most prevalent arthritis globally and represents a major challenge for twenty-first century health care systems.[1,2] The Global Burden of Disease 2020 report showed an increase of 9.3% and 8.2% in the age-standardized OA point prevalence and annual incidence rate from 1990 to 2017.[3] The prevalence rises with increasing age; in the USA (United States of America), OA was found in 13.9% of adults aged ≥25 years and 33.6% for those aged ≥65 years respectively in 2005.[4] The lifetime risk of having symptomatic knee OA is about 40% in men and 47% in women, and the risk increases to 60.5% among obese persons.[5] By the year 2040, an estimated 25.9% of the total adult population will have doctor-diagnosed arthritis in the USA.[6]

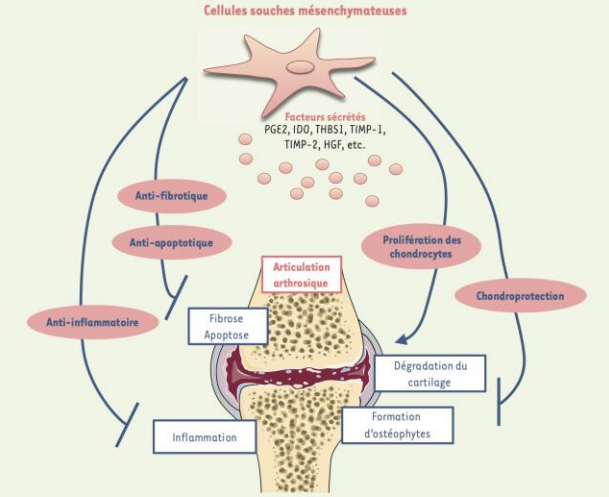
Globally, 80% of patients with OA suffer from limitations in movement, and 25% from difficulty in performing their major daily activities of life; representing a significant impact of OA on functional impairment and disability.[7] In terms of economic burden, mean per-person earnings losses caused by OA were, on average, 7548 US$ per year from 2008 to 2011.[8] The mean all-cause health care utilization of working-age patients with OA is $14,521 US$ per year.[9] The socio-economic costs of OA were reported to range between 0.25% and 0.50% of a country's GDP.[10] In an individual patient data meta-analysis, the pooled estimate for

Propriétés des cellules souches mésenchymateuses

PHARMACODYNAMIE

DMOAD ?
DISEASE MODIFYING OSTEOARTHRITIS DRUGS

= Traitements + efficaces et disruptifs ?
Ambition:
Agir à la fois sur la douleur
et sur les changements structurels,
afin de prévenir et/ou de guérir l'arthrose.



CIBLAGE CLINIQUE ET STRUCTURAL

DOULEURS

Anomalies structuro-fonctionnelles des tissus de l'articulation

- Modèles animaux inadaptés
- Inhibiteur IL-1: échec
- Sprifermine = FGF-18 recombinant
- **Liraglutide**: analogue GLP-1
- **LNA043**: dérivé de l'angiopoïétine-like 3
- Chondroprotecteurs ??

☞ ! L'effet antalgique d'un médicament dans l'arthrose doit être contrôlé pour éviter des phénomènes de destruction accélérée.

Injections de « cellules souches » ?

- **Cellules souches = cellules aux potentialités multiples, essentiellement immunomodulatrices et régénératrices**

- **Source des cellules souches méchenchymateuses**
  - **Moelle osseuse = bone marrow Mesenchymal Stem Cells (MSCs),**
  - **Tissu adipeux = Adipose-derived Stem Cells (ASCs)**
  - **Cordon ombilical : umbilical Stem Cells (ChordSCs)**
  - **Membrane et liquide synovial**
  - **iPS (Induced pluripotent stem cells)**

=> L'obtention de cellules souches nécessite une étape d'isolement et d'amplification in vitro, peu compatible avec l'environnement d'un bloc opératoire

L'étude Princeps chez l'Homme

- Essai clinique ADIPOA (2012-2014). 18 patients volontaires avec arthrose du genou.
  - Réponse positive chez 80% des patients : augmentation de la fonction et de la mobilité des articulations + baisse significative de la douleur neuf mois après l'injection IA
  - Amélioration la plus importante avec la plus faible dose de CSM ($2x10^6$ ASC autologues)
  - Aucun effet secondaire important local ou systémique

Y.-M. Pers, L. Rackwitz, R. Ferreira, O. Pullig, C. Delfour, F. Barry, L. Sensebe, L. Casteilla, S. Fleury, P. Bourin, D. Noël, F. Canovas, C. Cyteval, G. Lisignoli, J. Schrauth, D. Haddad, S. Domergue, U. Noeth, C. Jorgensen, ADIPOA Consortium, Adipose Mesenchymal Stromal Cell-Based Therapy for Severe Osteoarthritis of the Knee: A Phase I Dose-Escalation Trial, Stem Cells Transl. Med. 5 (2016) 847–856. https://doi.org/10.5966/sctm.2015-0245.

- Essai clinique ADIPOA-2 (2016-). 153 patients volontaires

F. Migliorini, B. Rath, G. Colarossi, A. Driessen, M. Tingart, M. Niewiera, J. Eschweiler, Improved outcomes after mesenchymal stem cells injections for knee osteoarthritis: results at 12-months follow-up: a systematic review of the literature, Arch. Orthop. Trauma Surg. 140 (2020) 853–868. https://doi.org/10.1007/s00402-019-03267-8.

Etude clinique – CSM du tissu adipeux et arthrose

Original Research

Evaluation of a Single Intra-Articular Injection of Autologous Adipose Tissue for the Treatment of Osteoarthritis: A Prospective Clinical Study in Dogs

Greta S. Pavarotti[1] Vincent Hivernaud[2] Mélanie Brincin[1] Régis Roche[2] Pierre Barreau[1] Franck Festy[2] Olivier Gauthier[1]

[1] Department of Small Animal Surgery and Anesthesia, ONIRIS Nantes Atlantic College of Veterinary Medicine, Nantes, France
[2] Stemcis Cyroi, 2 rue Maxime Rivière, 97490 Ste Clotilde, Ste Clotilde, France

Address for correspondence Greta S. Pavarotti, DVM, Department of Small Animal Surgery and Anesthesia, ONIRIS Nantes-Atlantic College of Veterinary Medicine, Food Science and Engineering, La, Chantrerie, CP 40706, 44307 Nantes Cedex 3, France (e-mail: gretapavarotti@gmail.com).

Vet Comp Orthop Traumatol

VCOT 2020. Pavarotti G et al.

Rationnel de l'utilisation du tissu adipeux

- Deux fractions dans le tissu adipeux:
  - Adipocytes matures
  - Fraction stromale vasculaire (SVF): un compartiment stromal et un compartiment hématopoïétique=> endothelial cells, pericytes, stromal cells and hematopoietic cells)
  - La moelle osseuse contient peu de cellules souches : sur 6 millions de cellules nucléées par millilitre, seulement 0.001 à 0.01% seraient des cellules souches

  ⇒ 500 à 1000 fois plus de CSM dans le TA versus MO

- Effets attendus en injection intra articulaire:

⇒ Activité anti-inflammatoire, immunomodulatrice, régénératrice

⇒ Lubrifiant

Etude clinique – CSM du tissu adipeux et arthrose

- Objectifs

➢ Quelle efficacité clinique du traitement intra articulaire de tissu adipeux ?

- Etude clinique prospective sur des chiens souffrant d'arthrose, une seule articulation ciblée

➢ Autorisation CERVO-2016-18-V du 15/12/2016

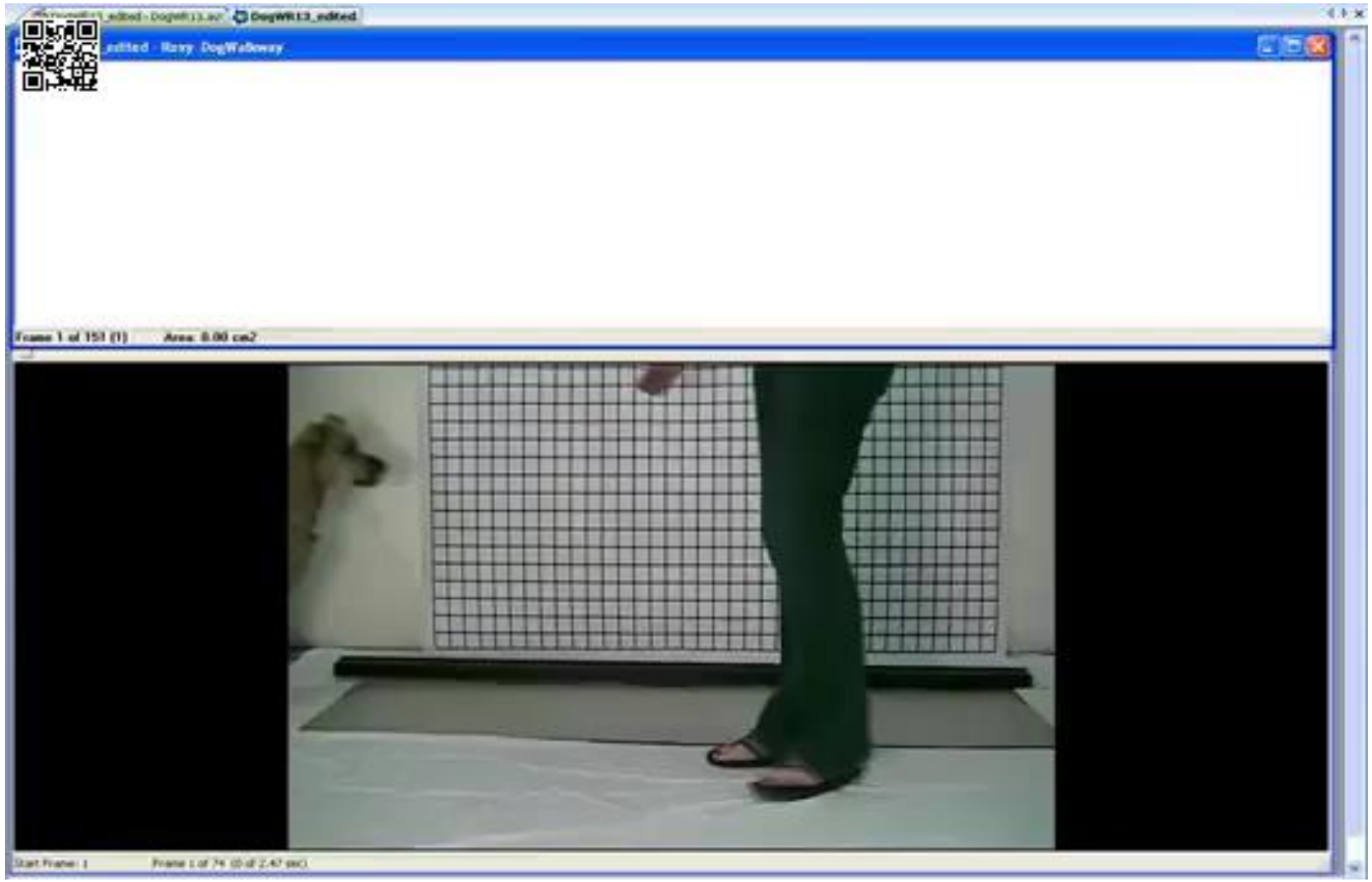
➢ Critères d'inclusion : arthrose clinique et radiographique

➢ Critères d'exclusion : traitement chirurgical antérieur, AINS et autres < 4 semaines

➢ Suivi sur 6 mois (1,2,5,9 et 12 semaines) : Score vétérinaire, Score CBPI (Canine Brief Pain Inventory): douleur & capacités motrices

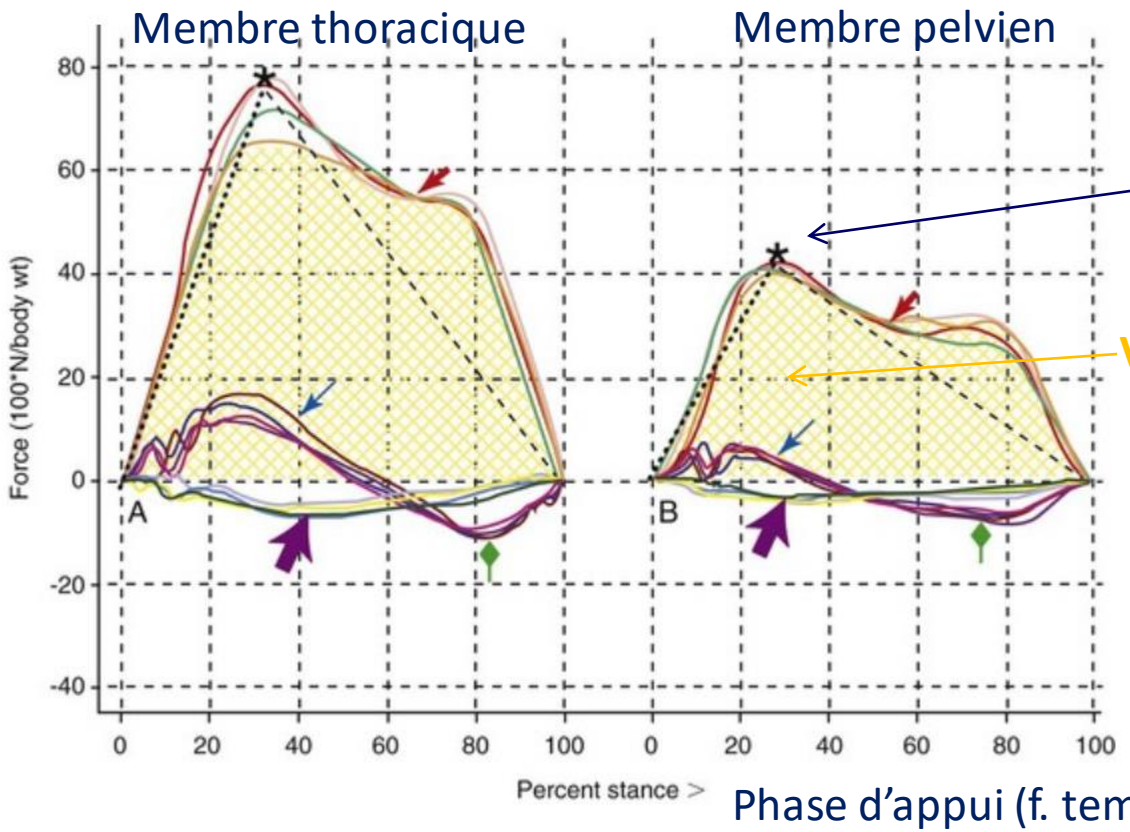
➢ Tapis de marche : Paramètres quantitatifs = Vertical Impulse (VI) et Peak Vertical Forces (PVF)

Longitudinal course: Walkway-assisted Gait Analysis



Tapis de marche « Pressure-sensitive »

Composantes verticales des forces de réaction du sol lors de l'appui



Peak vertical force

Vertical impulse (AUC)

FIGURE 74-2 Graphic representation of ground reaction forces at a walk for four trials. Each color represents a different trial. The forelimb **(A)** is represented first, followed by the hindlimb **(B).** The *red arrows* point to the vertical (Z) force graphs. *Blue arrows* point to the braking portion of the craniocaudal (Y) force graph, and the *green arrows* point to the propulsion portions of the Y force trace. The mediolateral (X) force trace is indicated by the wide *purple arrow*. The peak vertical force is labeled for the red trial with an *asterisk*. The vertical impulse is depicted for the gold trial by the *gold cross-hatched area* under the curve. The rising slope and the falling slope are depicted with a dotted *black line* and a *dashed black line*, respectively.

Etude clinique – CSM du tissu adipeux et arthrose

❑ 21 chiens inclus: 11 coudes, 8 hanches

	Joint	Diagnosis	Previous surgery
1	L hip	Hip osteoarthritis	No
2	L elbow	Medial compartiment disease	Arthroscopy 1 year before injection with fragment removal
3	L tarsus	Tarsal osteoarthritis	No
4	L hip	Hip osteoarthritis	No
5	R elbow	Medial compartiment disease	No
6	L elbow	Medial compartiment disease	No
7	R elbow	Medial compartiment disease	Arthroscopy 2 years before injection with fragment removal
8	L elbow	Elbow osteoarthritis	PRP injection one year before injection
9	L hip	Hip osteoarthritis	No
10	L elbow	Elbow osteoarthritis	No
11	R hip	Hip osteoarthritis	No
12	R elbow	Elbow osteoarthritis	No
13	L stifle	cranial cruciate ligament injury and chronic joint instability	No
14	R hip	Hip osteoarthritis	No
15	L elbow	Medial compartiment disease	No
16	L hip	Hip osteoarthritis	No
17	L elbow	Medial compartiment disease	No
18	L hip	Medial compartiment desease	No
19	R hip	Hip osteoarthritis	No
20	R elbow	Medial compartiment disease	Arthroscopy 2.5 years before with fragment removal
21	R elbow	Medial compartiment disease	Arthroscopy 1.5 years before with subtotal coronoidectomy

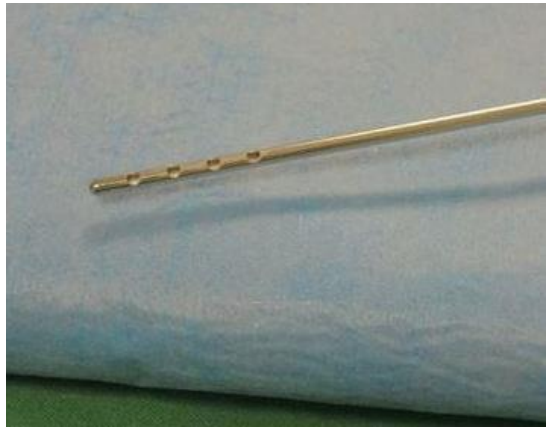
CAPdouleur
CHANGE ANIMAL PAIN

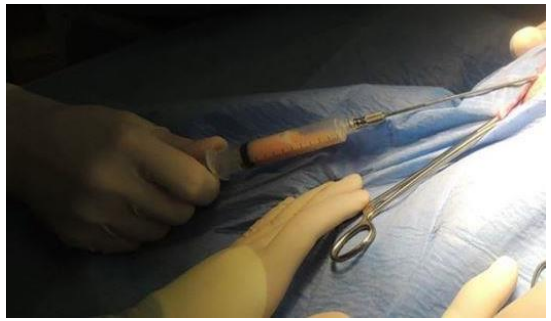
RÉPUBLIQUE FRANÇAISE
Liberté
Égalité
Fraternité

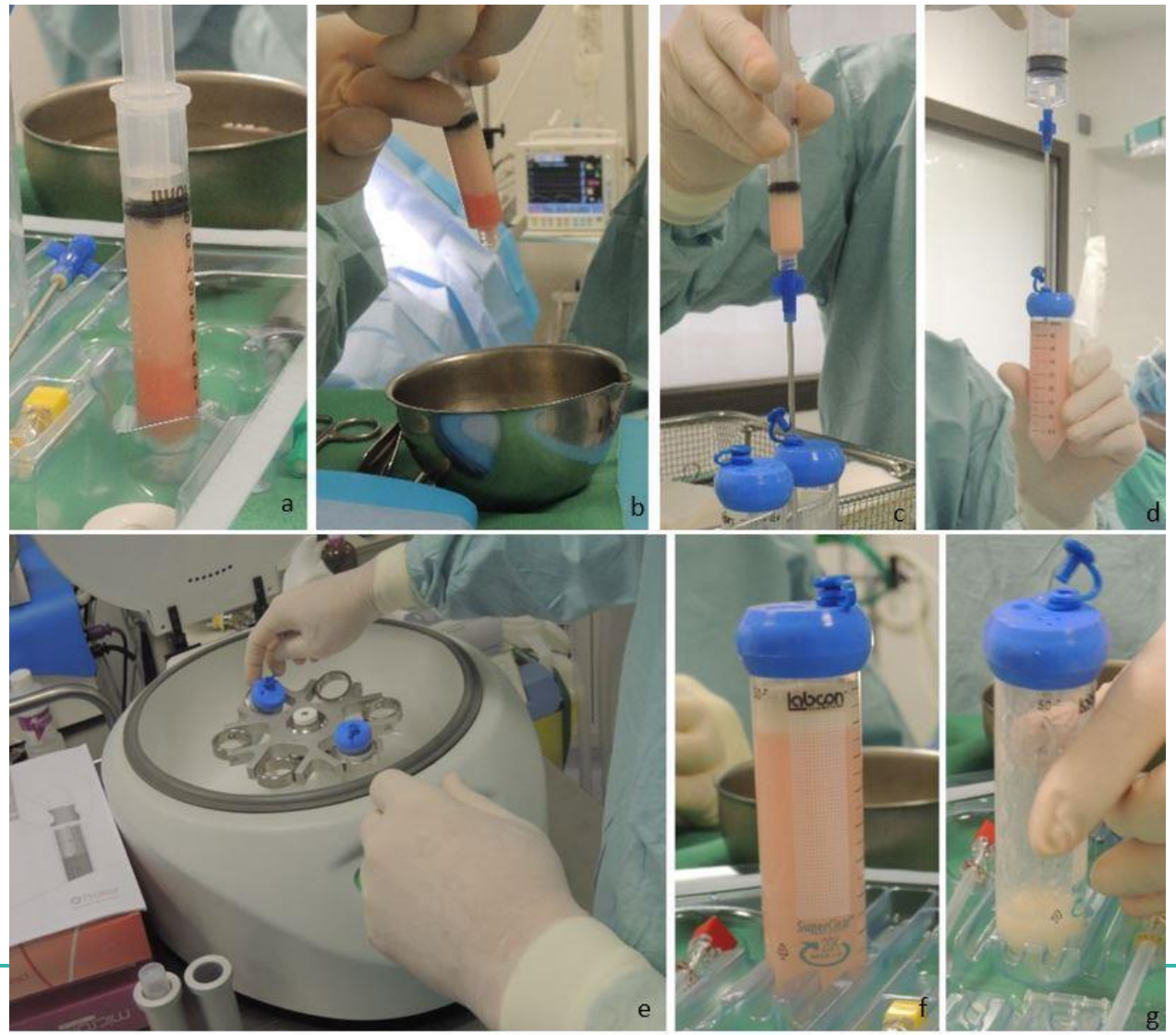
Oniris
ÉCOLE NATIONALE VÉTÉRINAIRE, AGROALIMENTAIRE ET DE L'ALIMENTATION

Etude clinique – CSM du tissu adipeux et arthrose

- Préparation

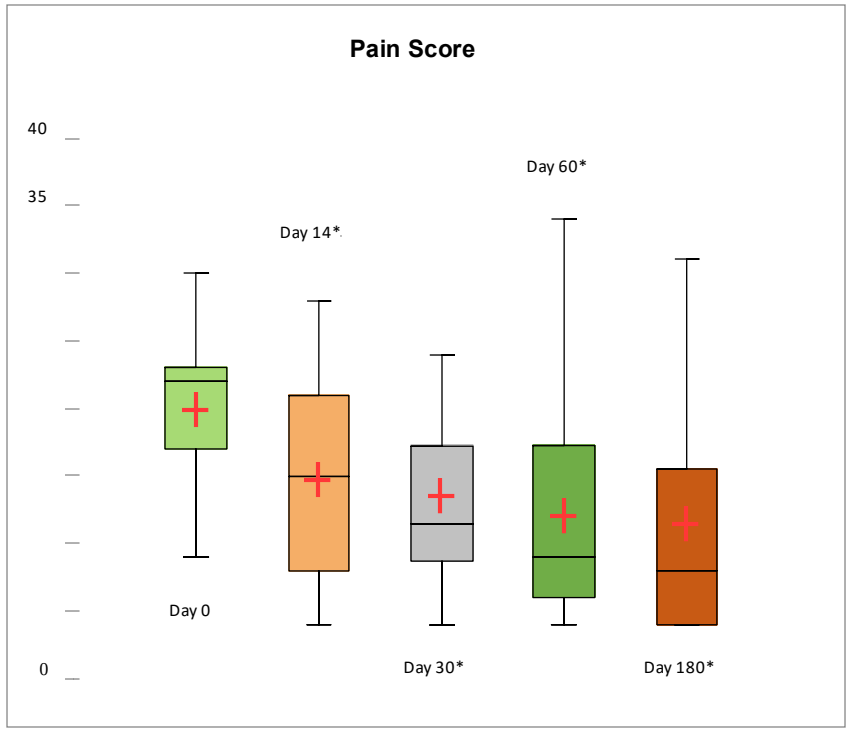


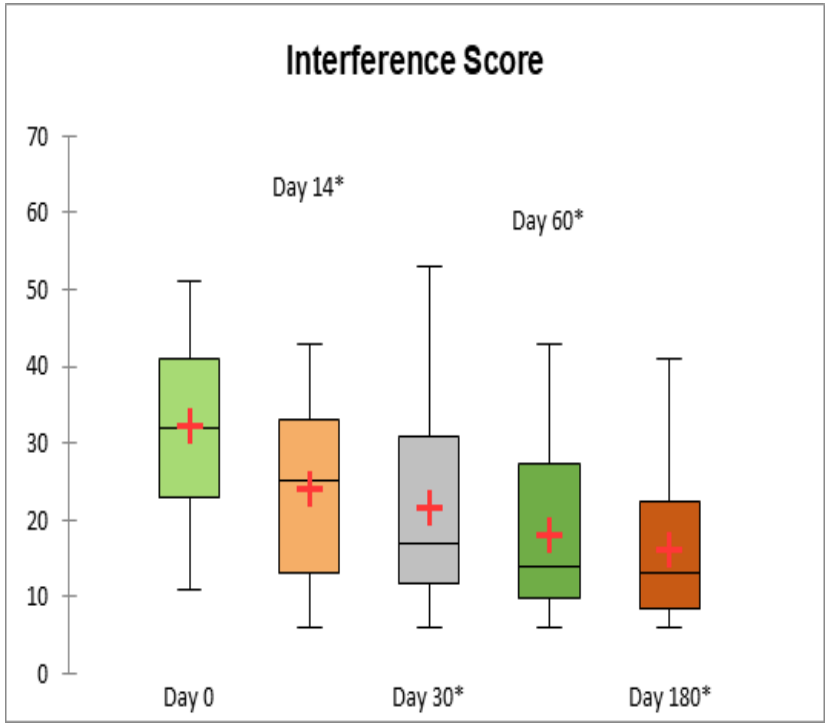




Etude clinique – CSM du tissu adipeux et arthrose

Evolution of CBPI Pain Score and Interference Score from day 0 (pre-injection) to day 180 post-injection

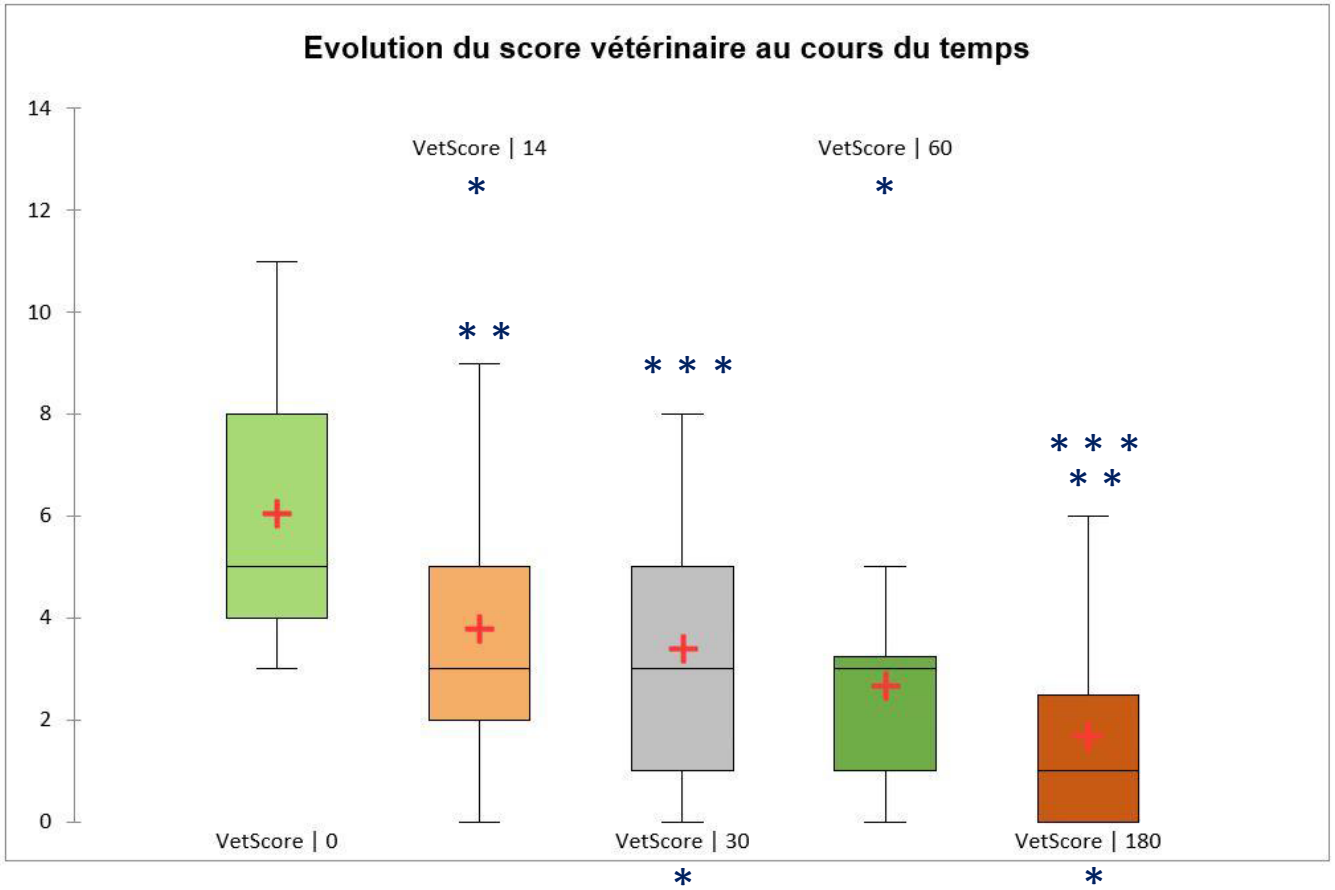




*Significant difference compared to day 0

Etude clinique – CSM du tissu adipeux et arthrose

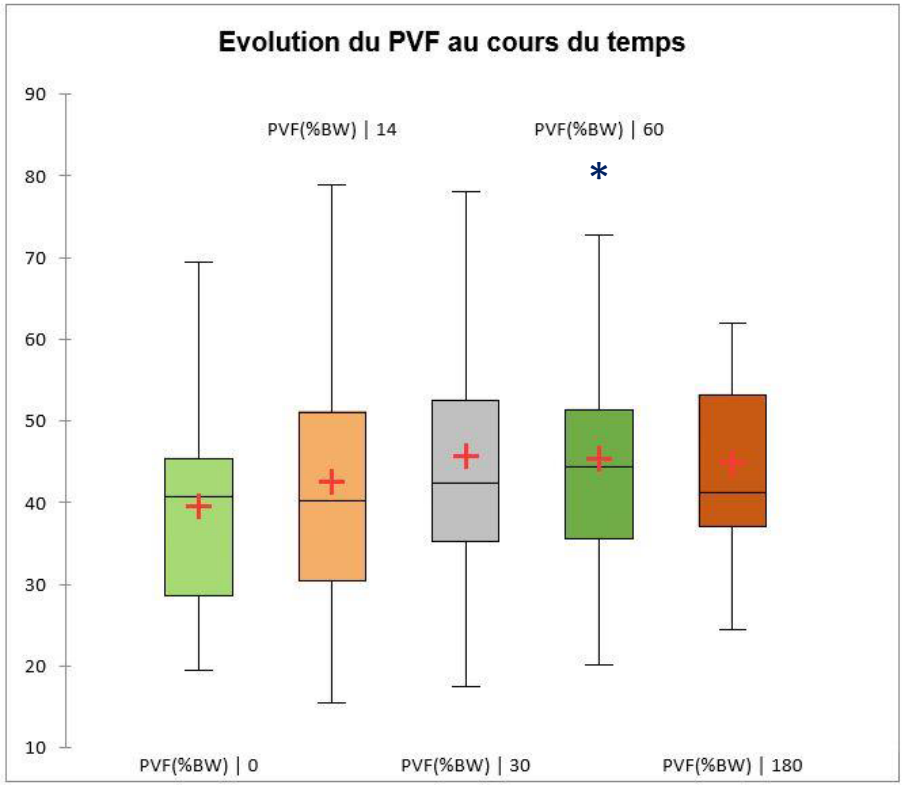
❑ Score vétérinaire

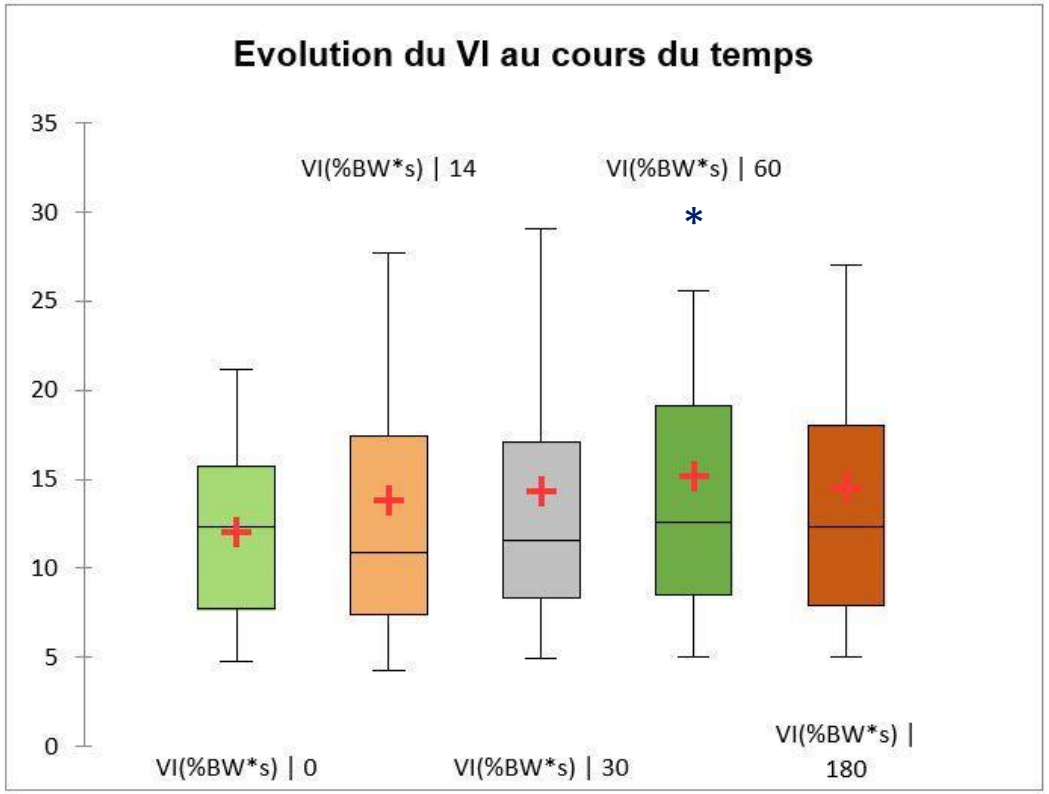


* Significant difference compared to day 0

Etude clinique – CSM du tissu adipeux et arthrose

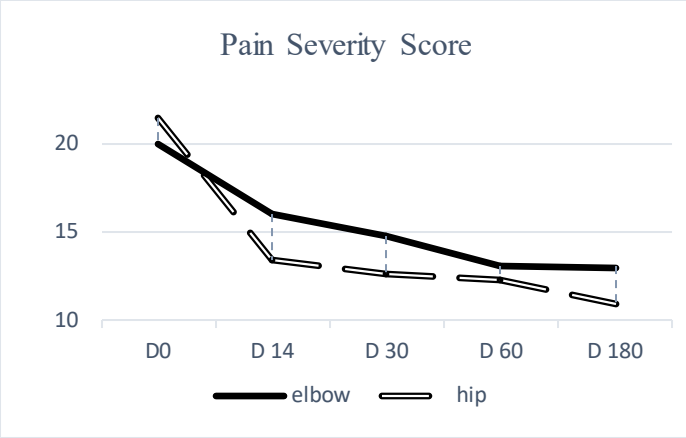
Evolution de PVF et VI de J0 (pré-injection) à J180 post-injection

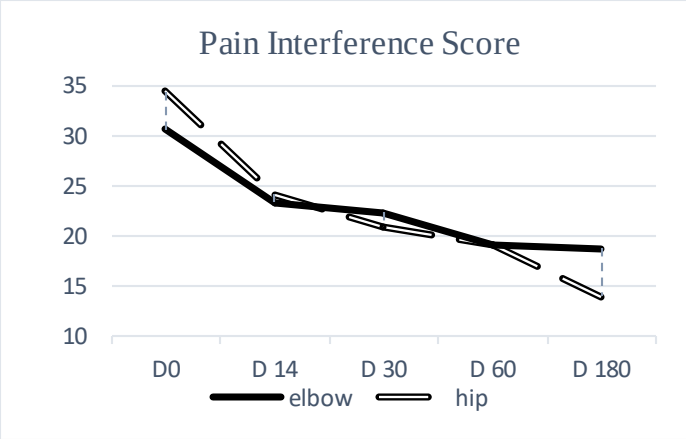




* Significant difference compared to day 0

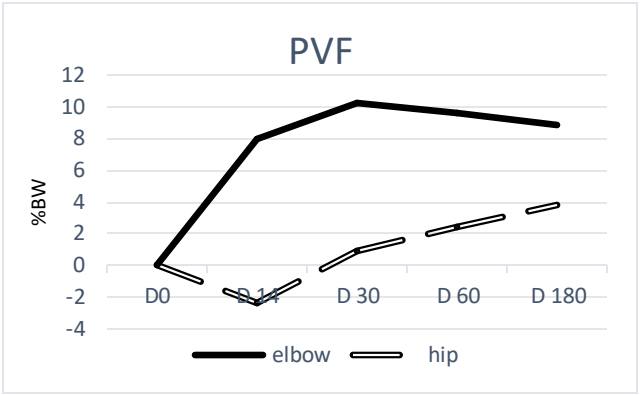
Etude clinique – CSM du tissu adipeux et arthrose

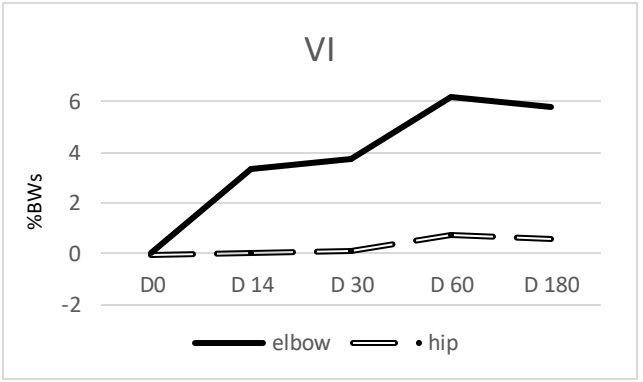


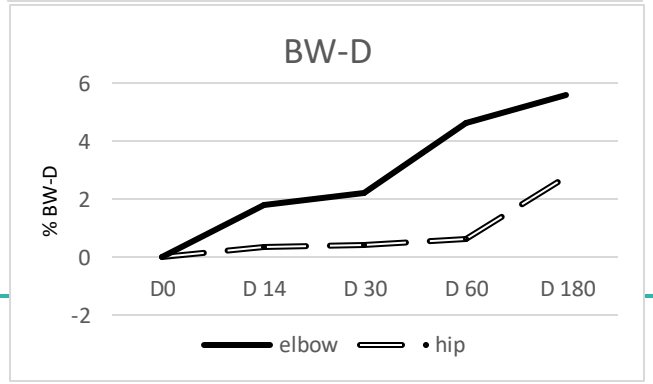


- Evolution des scores de douleur établis par le propriétaire (Canine Brief Pain Inventory)
- Evolution des paramètres locomoteurs
- En fonction de l'articulation cible : coude (n=11) versus hanche (n=8)

⇒ Effets bénéfiques significativement plus marqués pour le coude !







Etude clinique – CSM du tissu adipeux et arthrose

- Effets positifs mesurables pendant au moins 6 moins: diminution de la douleur, de la boiterie, amélioration de la qualité de vie
- Pas d'effets secondaires liés au prélèvement
- Pas de ré-injection, pas de nécessité de prise d'AINS pendant au moins 6 moins
- Effets différents en fonction de l'articulation traitée : coude > hanche
- Compatible avec une seule session opératoire d'environ 30 min.

Injections de « cellules souches » autologues

Vilar *et al. BMC Veterinary Research* 2014, **10**:143
http://www.biomedcentral.com/1746-6148/10/143

BMC Veterinary Research

RESEARCH ARTICLE Open Access

Assessment of the effect of intraarticular injection of autologous adipose-derived mesenchymal stem cells in osteoarthritic dogs using a double blinded force platform analysis

Jose M Vilar[1*], Miguel Batista[1], Manuel Morales[1], Angelo Santana[1], Belén Cuervo[2,3,4,5], Mónica Rubio[2,3,4,5], Ramón Cugat[3,4,6], Joaquín Sopena[2,3,4,5] and Jose M Carrillo[2,3,4,5]

Abstract

Background: Regenerative medicine using Mesenchymal Stem Cells (MSC) alone or combined with Plasma Rich in Growth Factors (PRGF) is a rapidly growing area of clinical research and is currently also being used to treat osteoarthritis (OA). Force platform analysis has been consistently used to verify and quantify the efficacy of different therapeutic strategies for the treatment of OA in dogs including MSC associated to PRGF, but never with AD-MSC alone.
The aim of this study was to use a force platform to measure the efficacy of intraarticular ADMSC administration for limb function improvement in dogs with severe OA.

Results: Ten lame dogs with severe hip OA and a control group of 5 sound dogs were used for this study. Results were statistically analyzed to detect a significant increase in peak vertical force (PVF) and vertical impulse (VI) in treated dogs. Mean values of PVF and VI were significantly improved within the first three months post-treatment in the OA group, increasing 9% and 2.5% body weight, respectively, at day 30. After this, the effect seems to decrease reaching initial values.

Conclusion: Intraarticular ADMSC therapy objectively improved limb function in dogs with hip OA. The duration of maximal effect was less than 3 months.

- BMC Vet Res 2014

- Cellules souches ADSC autologues
- 10 chiens avec boiterie liée à arthrose de la hanche
- Evaluation subjective via tapis de marche
- Effet décroissant après un mois, pas d'effet au-delà de 3 mois

Injections de « cellules souches » allogéniques

Long-Term Safety and Efficacy of Single or Repeated Intra-Articular Injection of Allogeneic Neonatal Mesenchymal Stromal Cells for Managing Pain and Lameness in Moderate to Severe Canine Osteoarthritis Without Anti-inflammatory Pharmacological Support: Pilot Clinical Study

https://www
ull

*Quentin Cabon[1], Marine Febre[2], Niels Gomez[1], Thibaut Cachon[1,3], Paul
Claude Carozzo[1,3], Nathalie Saulnier[2], Clément Robert[2], Véronique Live
Rodolphe Rakic[2], Nadia Plantier[2], Philippe Saas[4], Stéphane Maddens[2†] and
Eric Viguier[1,3*†]*

[1] Université de Lyon, VetAgro Sup, Centre Hospitalier Universitaire Vétérinaire, Marcy-l'Étoile, France, [2] Vetbiobank SAS, Marcy-l'Étoile, France, [3] Université de Lyon, VetAgro Sup, Interaction Cellule Environnement, ICE, Marcy-l'Étoile, France, [4] INSERM, EFS BFC, UMR1098, Interactions Hôte-Greffon-Tumeur, Ingénierie Cellulaire et Génique, Université Bourgogne Franche-Comté, Besançon, France

Objective: To explore the long-term safety and efficacy of canine allogeneic mesenchymal stromal cells (MSC) administered intra-articularly as single or repeated injections in appendicular joints of dogs affected by moderate to severe refractory osteoarthritis.

Study Design: 22 pet dogs were recruited into a non-randomized, open and monocentric study initially administering one cellular injection. A second injection was offered after 6 months to owners if the first injection did not produce expected results.

Materials and Methods: Anti-inflammatory treatment (if prescribed) was discontinued at last one week before the onset of treatment. Each injection consisted of at least 10 million viable neonatal allogeneic mesenchymal stromal cells obtained from fetal adnexa. Medical data was collected from veterinary clinical evaluations of joints up to 6 months post-injection and owner's assessment of their dog's mobility and well-being followed for a further 2 years when possible.

Results: Mild, immediate self-limiting inflammatory joint reactions were observed in 5/22 joints after the first injection, and in almost all dogs having a subsequent injection. No other MSC-related adverse medical events were reported, neither during the 6 months follow up visits, nor during the long-term (2-years) safety follow up. Veterinary clinical evaluation showed a significant and durable clinical improvement (up to 6 months) following MSC administration. Eight dogs (11 joints) were re-injected 6 months apart, sustaining clinical benefits up to 1 year. Owner's global satisfaction reached 75% at 2 years post-treatment

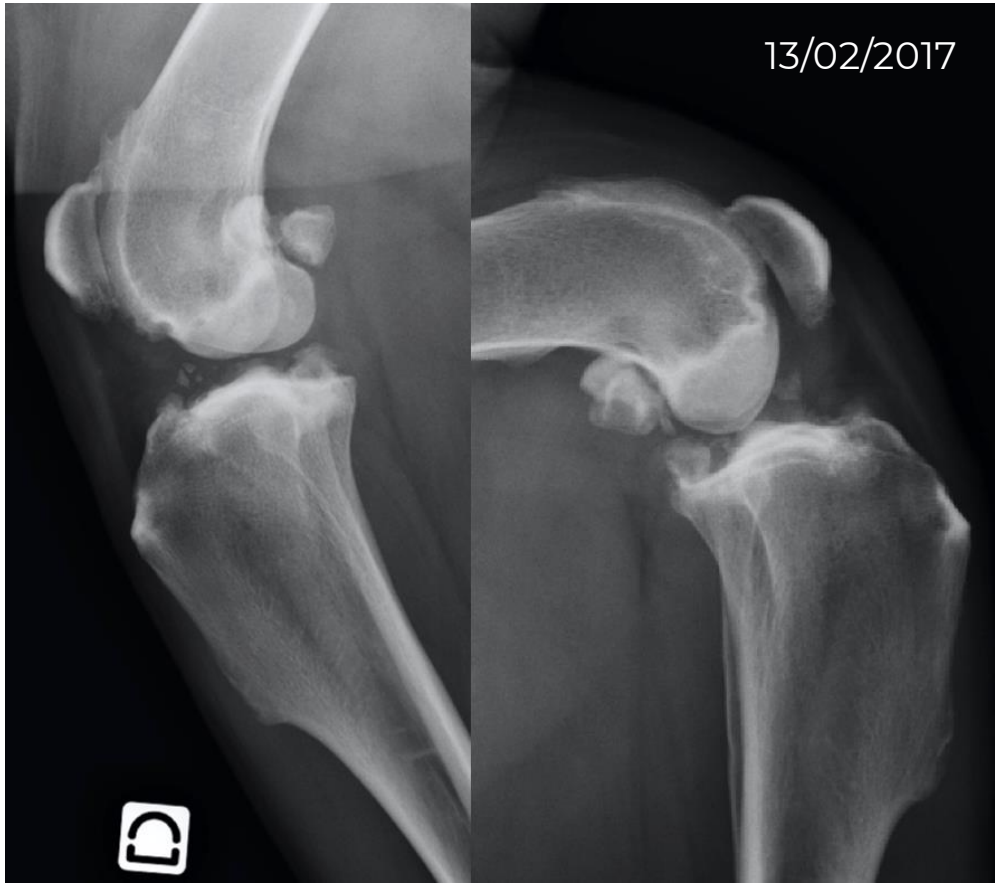
Conclusion: Our data suggest that a single or repeated intra-articular administration of neonatal MSC in dogs with moderate to severe OA is a safe procedure and confer clinical benefits over a 24-month period. When humoral response against MSC is investigated by flow cytometry, a positive mild and transient signal was detected in only one dog from the studied cohort, this dog having had a positive clinical outcome.

- ❑ Frontiers in Vet Science 2019

- ➢ Cellules isolées du cordon ombilical, allogéniques, lors de césarienne
- ➢ 22 chiens, diverses articulations
- ➢ Effets au moins pendant 6 mois, voire un an quand ré-injection
- ➢ 75% des propriétaires satisfaits à 2 ans post injection
- ➢ Pas d'effets indésirables de nature immunologique

Injections de « cellules souches » allogéniques: observations cliniques île de Ré

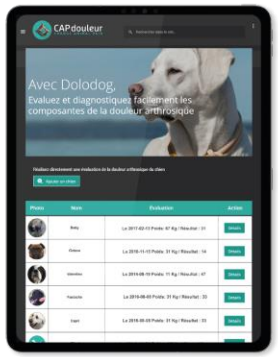
Betty Mastiff F 7 ans 67 kg - Arthrose Grassets D et G
Intolérance AINS - Double TPLO refusée - Tramadol BID

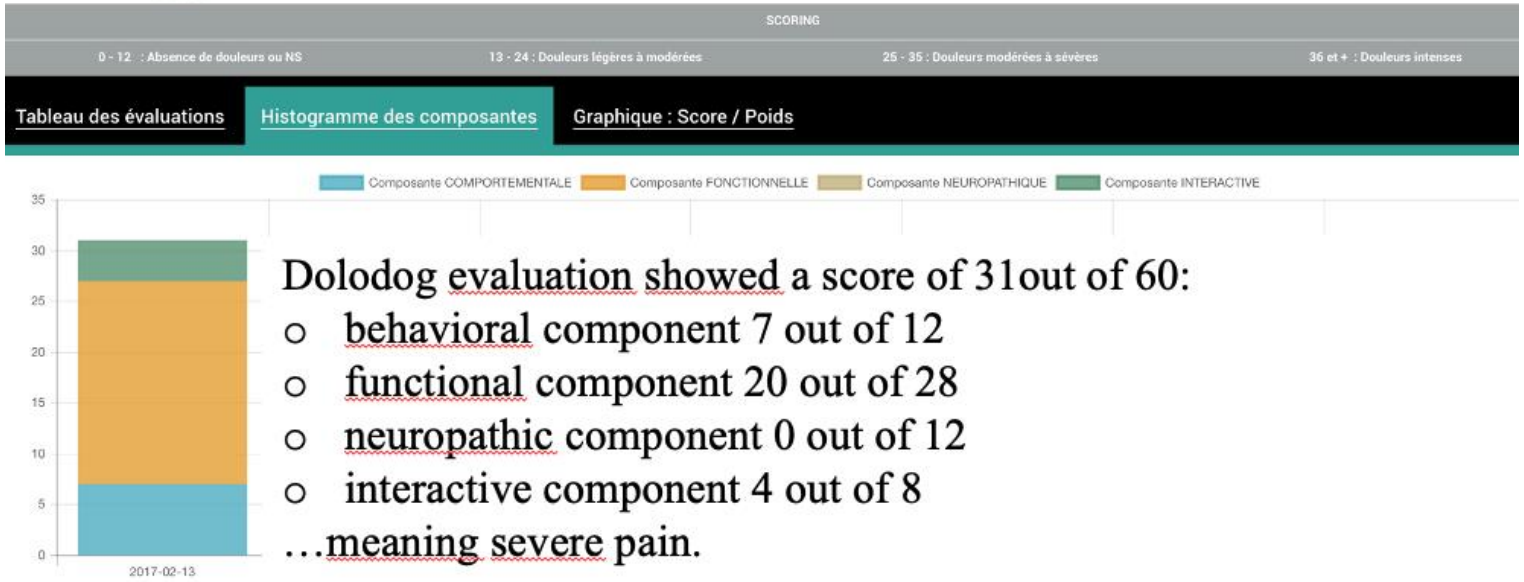


Injections de « cellules souches » allogéniques: observations cliniques île de Ré

Nom : Betty
Race : MASTIFF
Sexe : Femelle
Né le : 16 décembre 2009
Propriétaire : VATUS
Vétérinaire traitant : Dr Poitte

Modifier la fiche | Télécharger PDF | Nouvelle évaluation





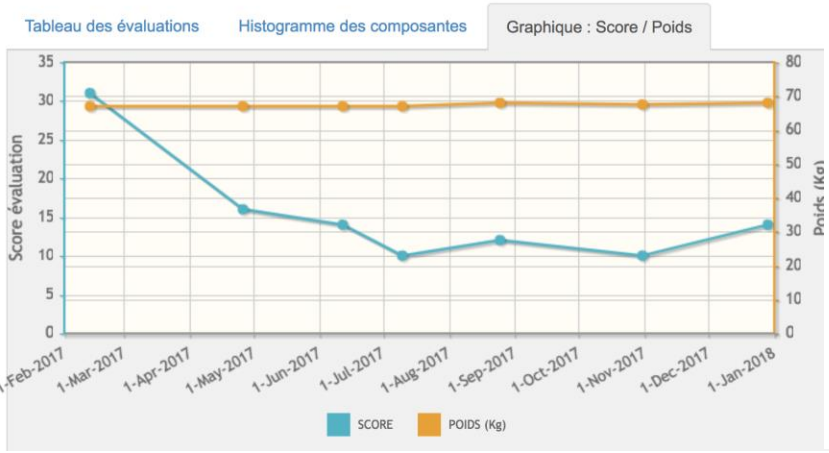
Dolodog evaluation showed a score of 31out of 60:

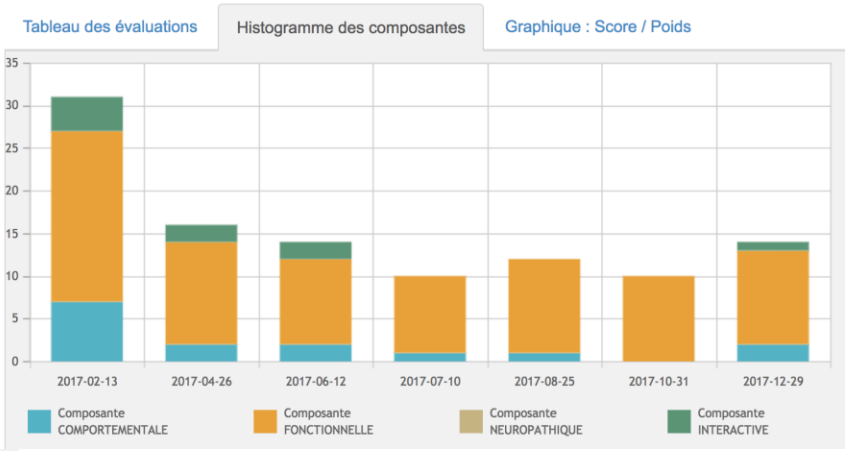
- behavioral component 7 out of 12
- functional component 20 out of 28
- neuropathic component 0 out of 12
- interactive component 4 out of 8

…meaning severe pain.

DOLODOG

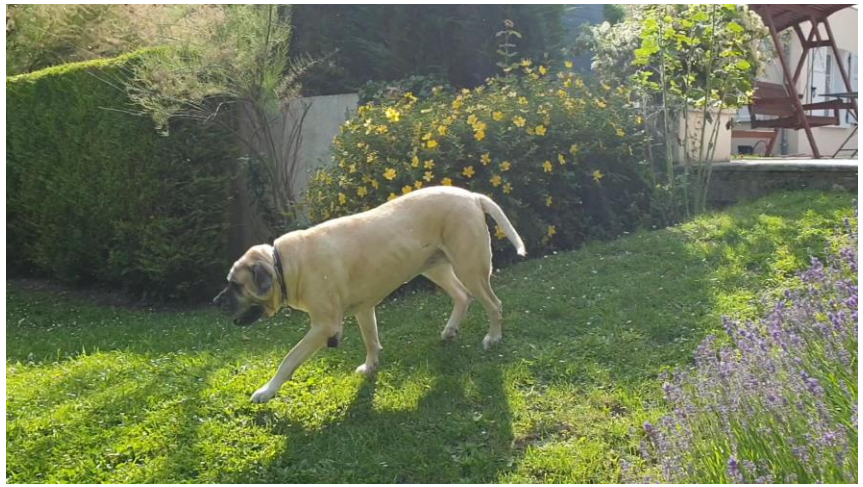
Injections de « cellules souches » allogéniques: observations cliniques île de Ré

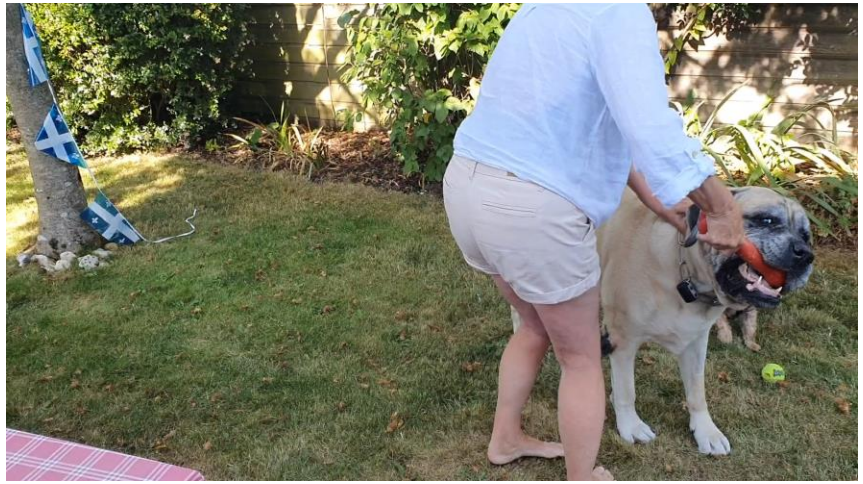




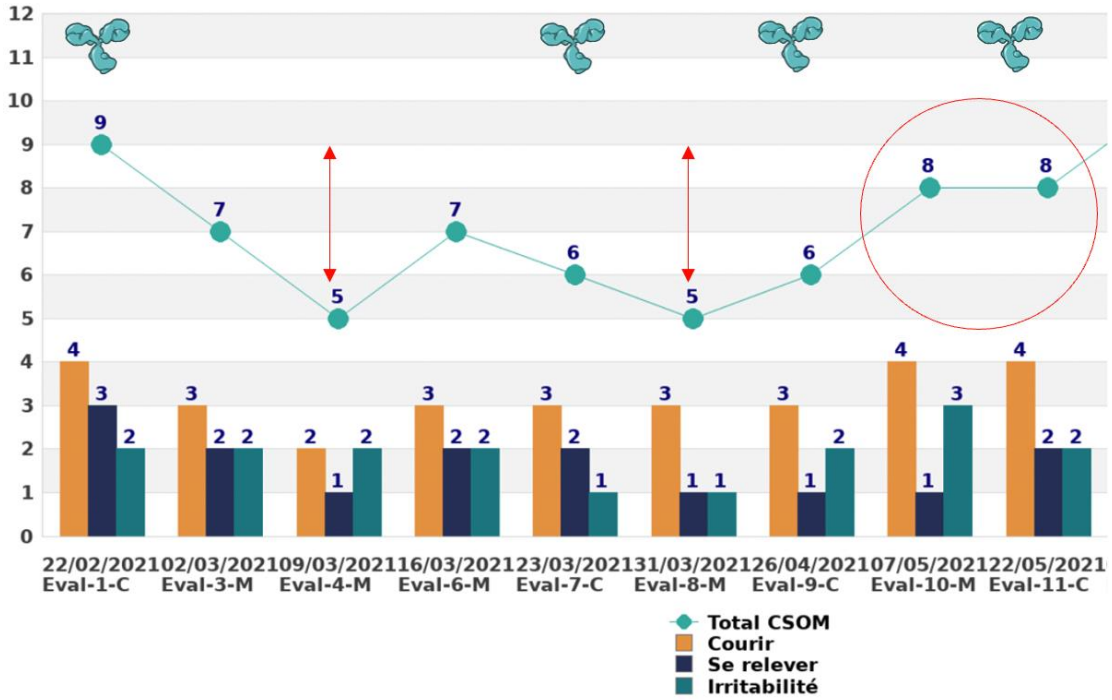
Injections de « cellules souches » allogéniques: observations cliniques île de Ré

+ 26 MOIS



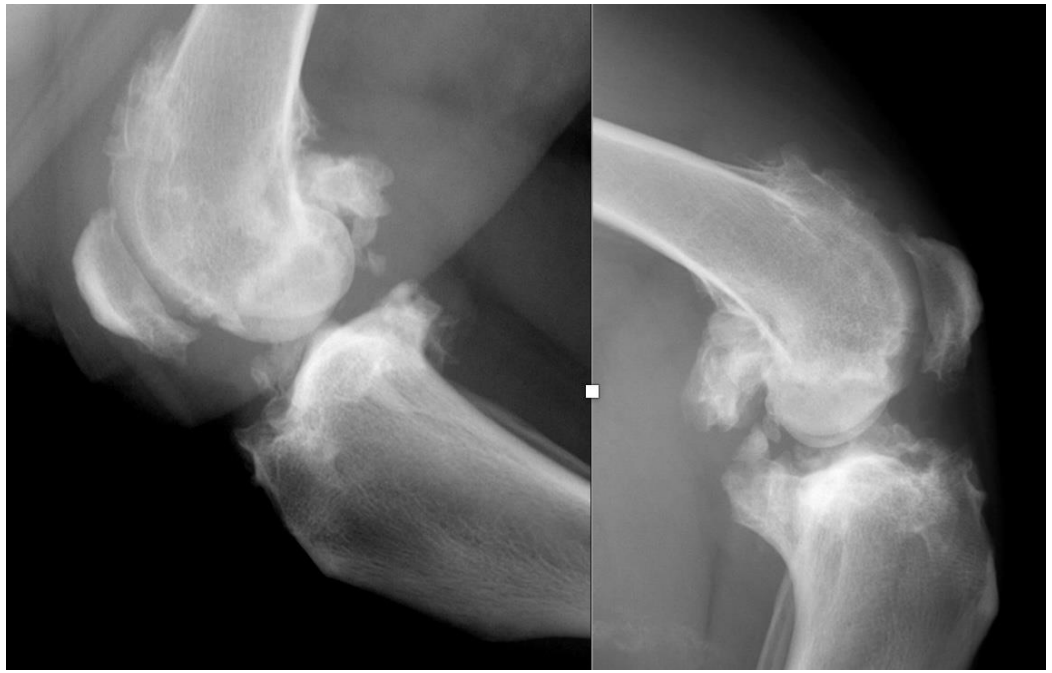


+ 3 ANS 3MOIS 11 ans

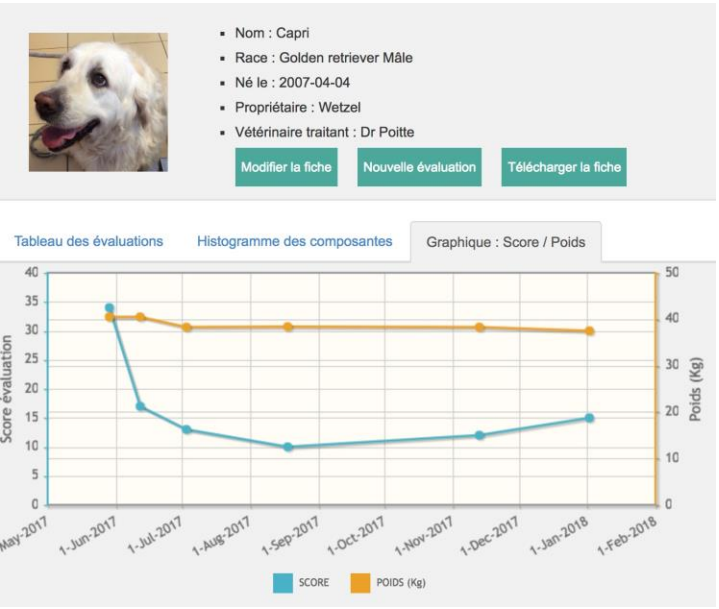


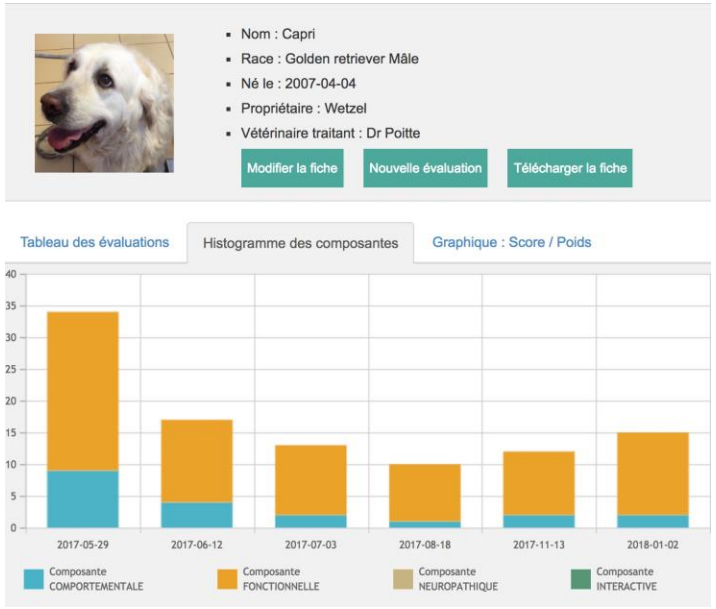
Injections de « cellules souches » allogéniques: observations cliniques île de Ré

Capri Retriever F 10 ans 38,3 kg
Arthrose Grassets D et G SB: 4 Dolodog: 34/60 Douleurs sévères



Injections de « cellules souches » allogéniques: observations cliniques île de Ré



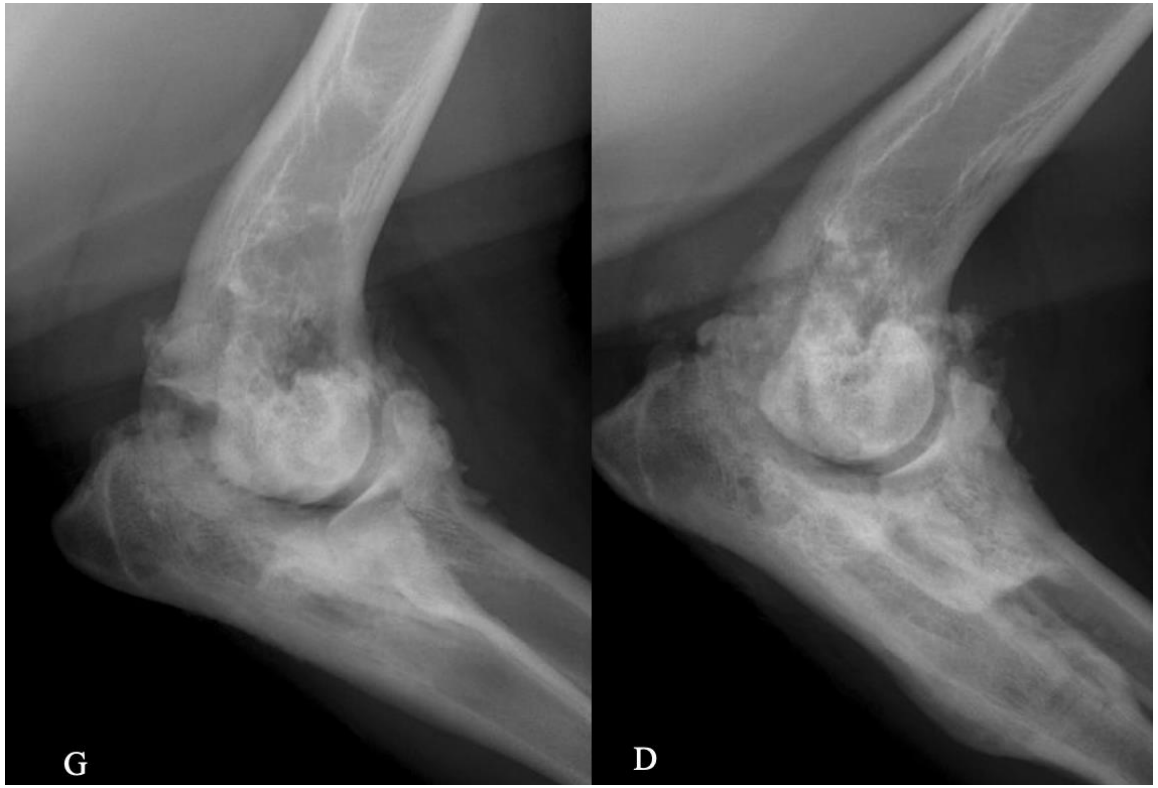


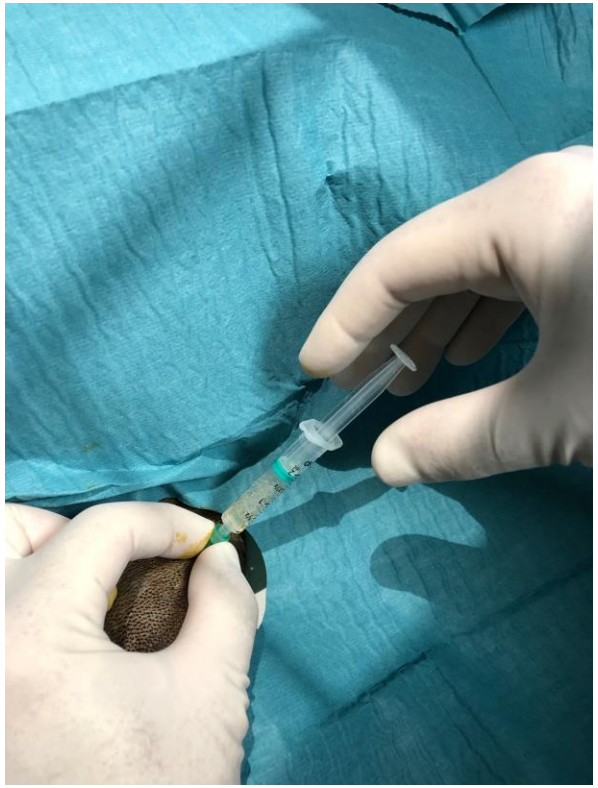
Injections de « cellules souches » allogéniques: observations cliniques île de Ré

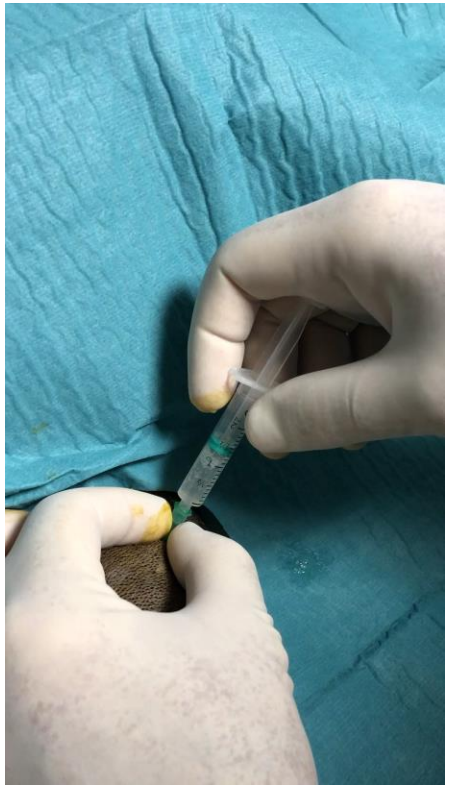
Hatchi Cane corso M 06/11/2012 7 ans 54 kg
Boiterie AD à 4 mois - Dysplasie coudes et hanches
Ostéotomie ulnaire D à 2 ans: Ondes de choc suite défaut cicatrisation
Douleurs post-opératoires chroniques:
Boiteries permanentes - SB: 3-4/5
Mavacoxib – Chondroprotecteurs – HA –Gabapentine - Amantadine

Injections de « cellules souches » allogéniques: observations cliniques île de Ré

1ère injection CSM néonatales allogéniques 13/08/2019 à 6 ans ½

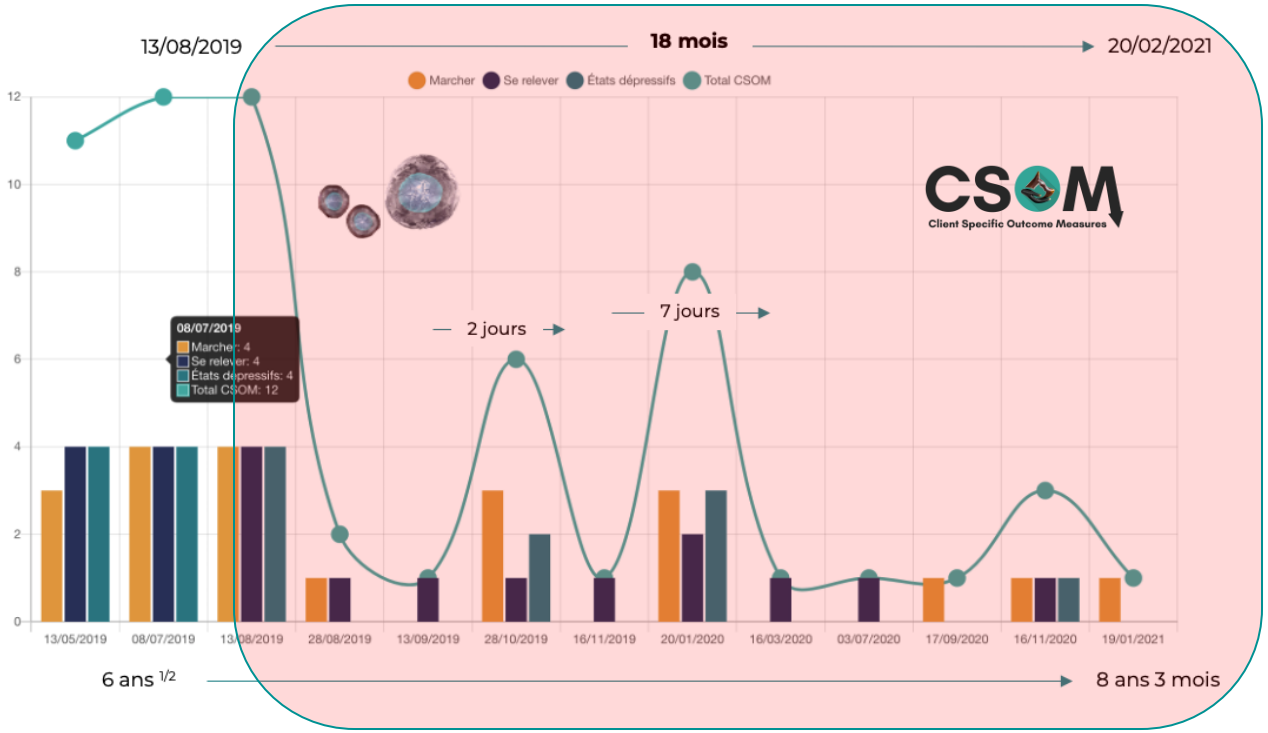


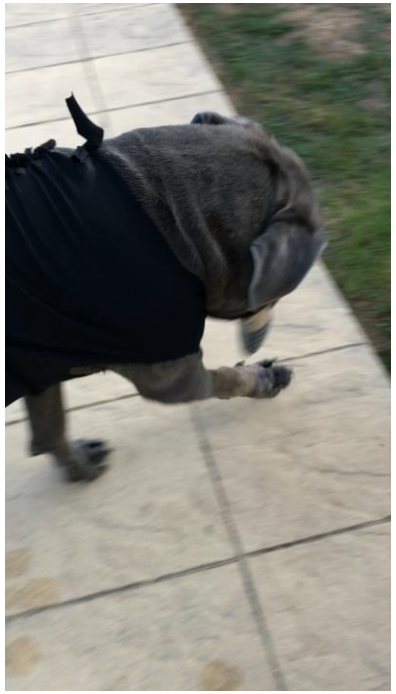




Injections de « cellules souches » allogéniques: observations cliniques île de Ré

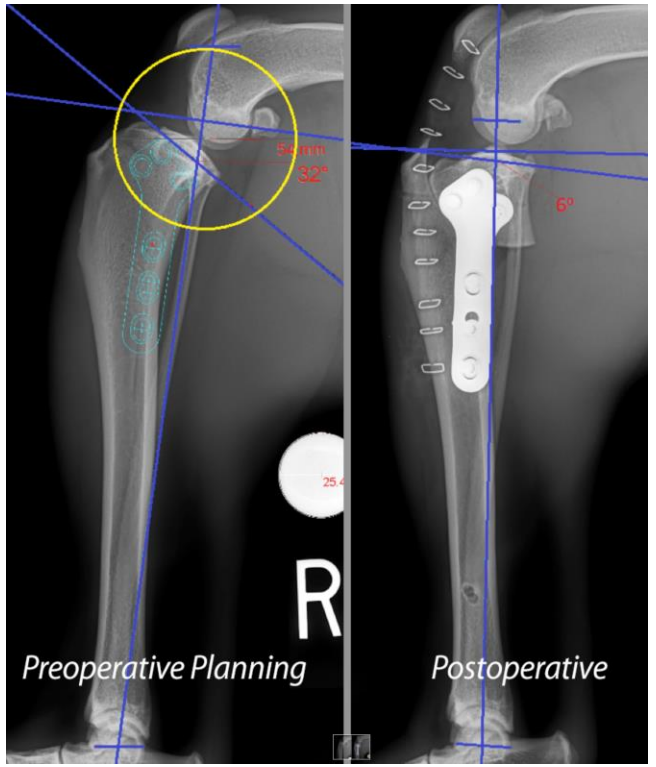
1ère injection CSM néonatales allogéniques 13/08/2019 à 6 ans 1/2





Injections de « cellules souches » allogéniques: observations cliniques île de Ré

Elfie Golden Retriever 7 ans 32 kg
Spondylose - Rupture LCA
Pivot shift (Instabilité en rotation interne du grasset)
Intolérance 2 AINS
Handicap fonctionnel et dégradation qualité de vie



Article

Complications associated with tibial plateau leveling osteotomy: A retrospective of 1519 procedures

Thomas J. Coletti, Mark Anderson, Mary Jean Gorse, Richard Madsen

Abstract — This retrospective study identified complications associated with tibial plateau leveling osteotomy (TPLO) and predisposing factors for these complications in a large population of dogs from a metropolitan area with cruciate ligament deficiency. There were 943 dogs that underwent unilateral TPLO and 288 with staged bilateral TPLO for a total of 1519 procedures. There were 47 cases with at least 1 major complication and 126 cases with at least 1 minor complication but no major complications. The total complication rate (major or minor) was 11.4% [95% confidence interval (CI) estimate: 9.8%, 13.2%]; the major complication rate was 3.1% (95% CI: 2.3%, 4.1%); and the minor complication rate was 8.3% (95% CI: 7.0%, 9.8%). Factors associated with development of complications included being a German shepherd dog [odds ratio (OR): 3.2], tibial plateau angle > 30° (OR: 1.6), and heavier weights (for every 4.5 kg increase in body weight the OR increased by 1.10). Tibial plateau leveling osteotomy is a common treatment for dogs with cruciate ligament deficiency and has a low complication rate.

Résumé — Complications associées à l'ostéotomie de nivellement du plateau tibial : rétrospective de 1519 interventions. Cette étude rétrospective a identifié les complications associées à l'ostéotomie de nivellement du plateau tibial (ONPT) et les facteurs de prédisposition pour ces complications dans une grande population de chiens atteinte d'une déficience du ligament croisé provenant d'une région métropolitaine. Il y avait 943 chiens qui avaient subi une ONPT unilatérale et en plusieurs temps pour un total de 1519 interventions. Il y a eu 47 cas avec au moins 1 complication majeure et 126 cas avec au moins 1 complication mineure mais aucune complication majeure. Le taux des complications totales (majeures ou mineures) était de 11,4 % [estimation de l'intervalle de confiance de 95 % (IC) : 9,8 %, 13,2 %]; le taux des complications majeures était de 3,1 % (IC de 95 % : 2,3 %, 4,1 %); et le taux des complications mineures était de 8,3 % (IC de 95 % : 7,0 %, 9,8 %). Les facteurs associés au développement des complications incluaient être un chien Berger allemand [rapport des cotes (RC) : 3,2], un angle du plateau tibial de > 30° (RC : 1,6) et des poids supérieurs (pour chaque hausse de 4,5 kg du poids corporel, le RC augmentait de 1,10). L'ostéotomie de nivellement du plateau tibial est un traitement commun chez les chiens avec une déficience du ligament croisé et elle présente un faible taux de complications.

(Traduit par Isabelle Vallières)

Can Vet J 2014;55:249–254

Introduction

Cranial cruciate ligament rupture (CCLR) is the most common cause of lameness in dogs (1). Numerous techniques have been described to address this condition. Among board-certified surgeons, the tibial plateau leveling osteotomy (TPLO) is one of the more popular techniques for treating cranial cruciate ligament (CCL) rupture (2).

Many studies have reviewed the clinical outcome of using TPLO to stabilize CCL deficient stifles. Complication rates in these studies ranged from 14.8% (a single surgeon in a private referral facility) (3) to 28.8% (multiple surgeons in a university teaching hospital) (4). Our purpose was to characterize the nature and the rate of short-term complications associated with the TPLO technique in a large number of cases performed by multiple experienced surgeons and to identify factors that might predispose to complications.

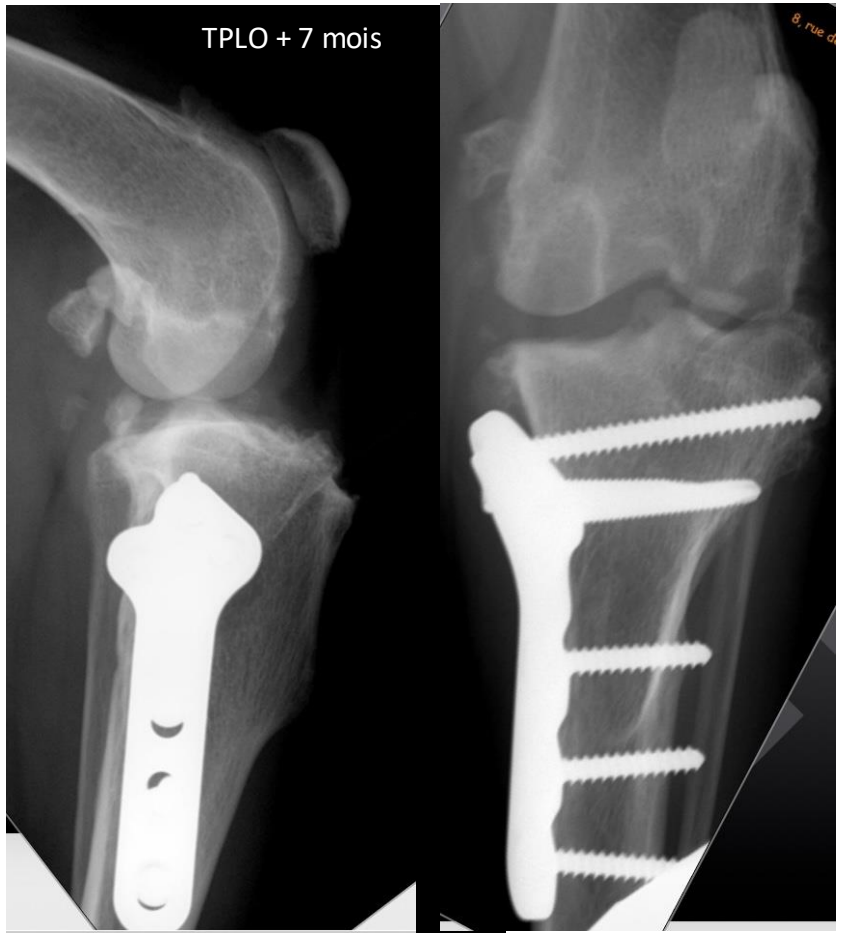
Materials and methods

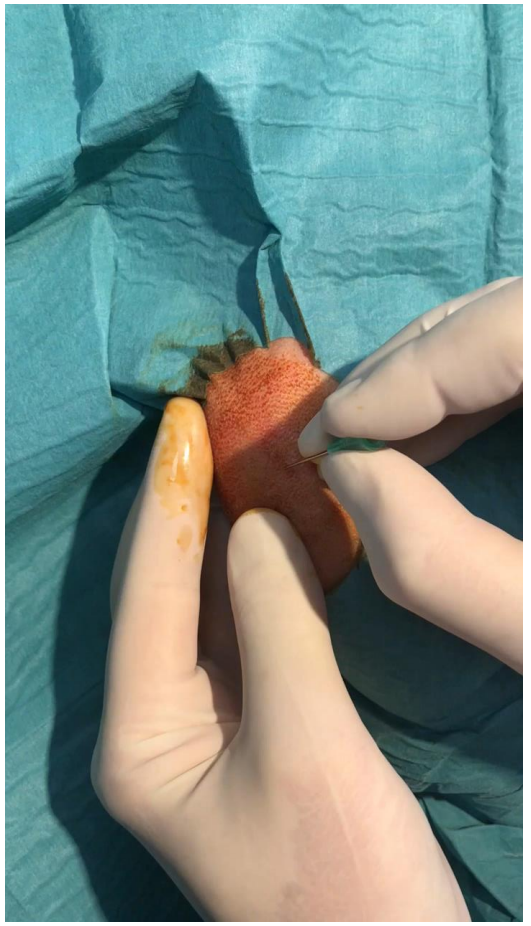
Medical records for all TPLO procedures performed at Veterinary Specialty Services in St. Louis, Missouri from January 2005 to January 2010 were reviewed. Criteria for inclusion included a

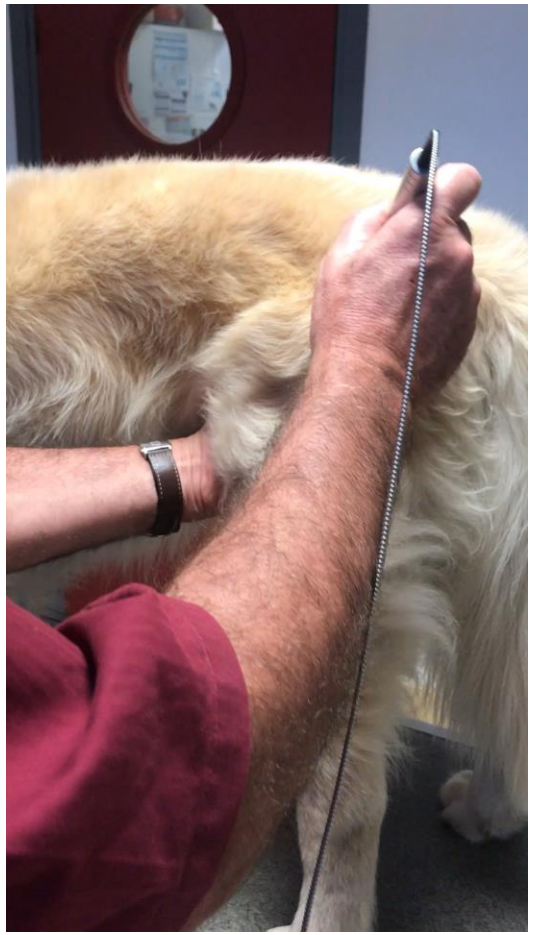
Veterinary Specialty Services, 1021 Howard George Drive, St. Louis, Missouri 63021, USA (Coletti, Anderson, Gorse); Department of Statistics, University of Missouri, Columbia, Missouri 65211, USA (Madsen).

Address all correspondence to Dr. Thomas Coletti; e-mail: drtcoletti@vssstl.com

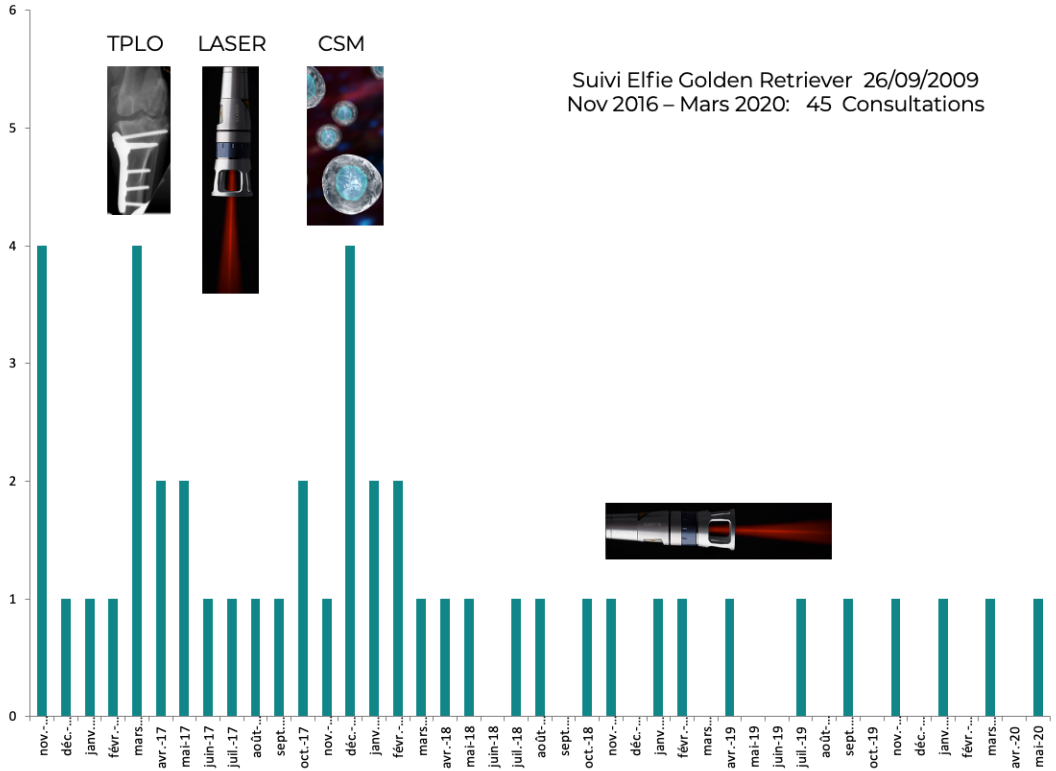
Injections de « cellules souches » allogéniques: observations cliniques île de Ré







Injections de « cellules souches » allogéniques: observations cliniques île de Ré



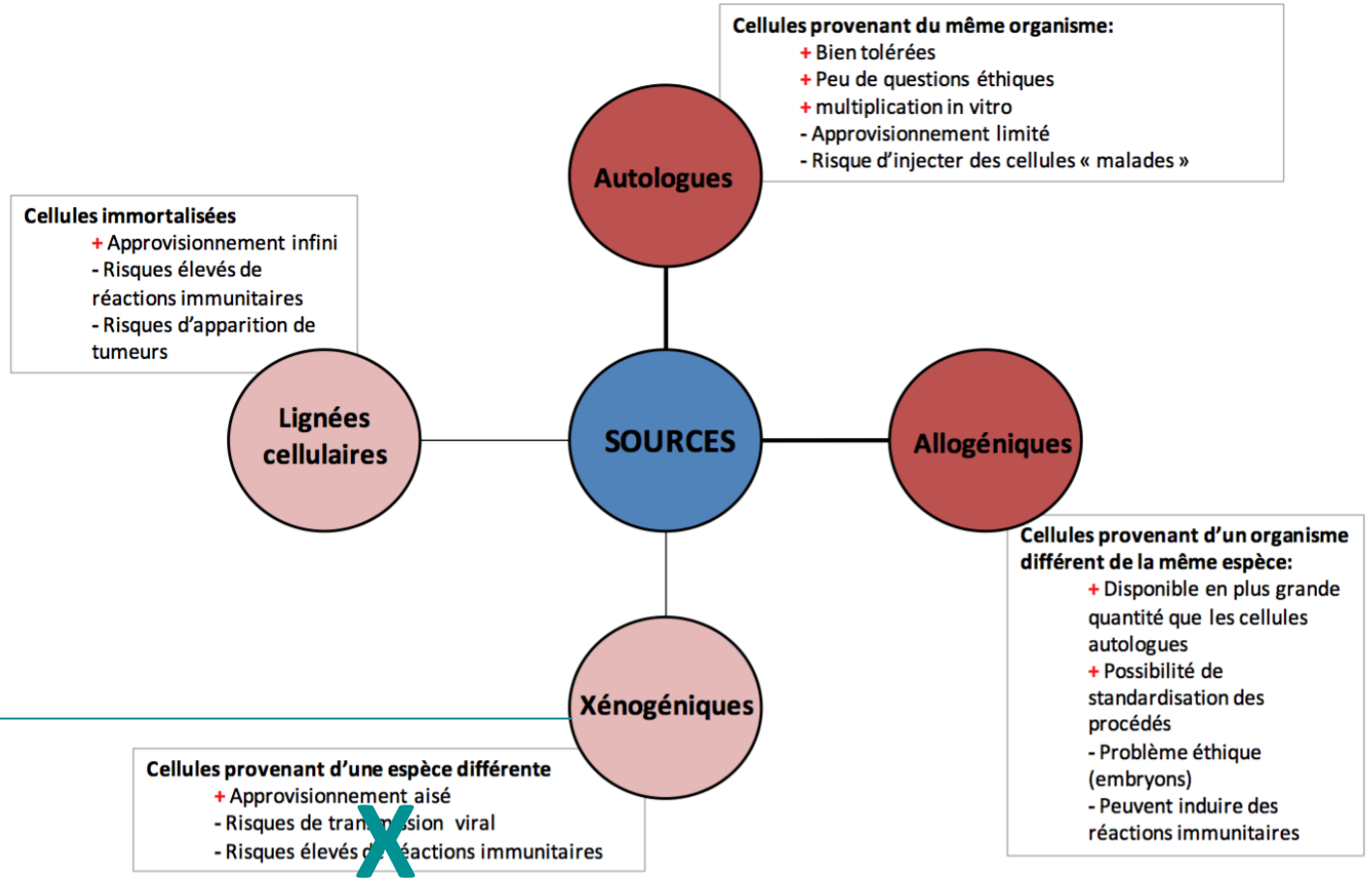
Injections de « cellules souches » allogéniques: observations cliniques île de Ré

+ 15 mois

+ 26 mois

Injections de « cellules souches » xénogéniques

DogStem® contient 7,5 millions de CSM du cordon ombilical équin
À très faible immunogénicité



Injections de « cellules souches » xénogéniques

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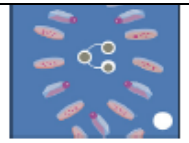

Original Article

Clinical results following intra-articular injection of adipose-derived stromal vascular fraction cells in patients with osteoarthritis of the knee

Naomasa Yokota*, Masayuki Yamakawa, Tomohiko Shirata, Tetsuya Kimura, Hideto Kaneshima

Tokyo Knee Osteoarthritis Clinic, Ichibankan building 7F, 5-3-12, Ginza, Chuo-ku, Tokyo 104-0061, Japan

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ABSTRACT

Background: The purpose of this study was to evaluate the clinical results following intra-articular knee injection of Stromal Vascular Fraction (SVF cell therapy).
Methods: This study involved 13 consecutive patients who had received SVF cell therapy at our clinic before November 2015 and completed the 6-month post-treatment follow-up period. For each treatment, approximately 200 mL or more of subcutaneous adipose tissue was harvested using tumescent liposuction technique and manual aspiration of tissue from the lower abdomen using a suction cannula under local anesthesia in the operating room. The adipose tissue harvested was processed using the Celution Centrifuge IV in the cell processing room of our clinic. These cells were injected into the articular cavity of both knees directly. Outcome was assessed on the basis of patient questionnaires using VAS for pain, the Japanese Knee Osteoarthritis Measure (JKOM), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).
Results: The 13 patients (26 knee joints), consisting of 2 men and 11 women, had a mean age of 74.5 ± 5.4 years. Eleven patients (9 women, 2 men) presented Grade IV knee OA according to the KL classification. The remaining two patients, both women, had Grade III. Pre-operative scores of JKOM, WOMAC, VAS, and BS-POP (for patients) were 55.9 ± 21.0, 49.6 ± 20.4, 72.7 ± 18.2, and 18.5 ± 2.0. No serious adverse events were reported. One month after injection of SVF, all the scores of JKOM, WOMAC, and VAS were significantly improved over baseline ($P < 0.01$). Ultimately, the scores were improved by an average of 35% over baseline for JKOM, 32% improvement in WOMAC, and 40% for pain (VAS).
Conclusions: Our approach is unique in that it occurred within the context of the recently enacted Japanese Regenerative Medicine Safety Act which is the first in the world.

- **Regen Ther 2017**
  - **Fraction stromale vasculaire de tissu adipeux autologue chez 13 patients de 75 ans d'âge moyen, souffrant d'arthrose du genou (26 articulations)**
  - **Amélioration de tous les scores cliniques et imagerie de 35% à un mois post injection**
  - **Amélioration mesurable jusqu'à 6 mois**
  - **Pas d'effets indésirables**

Conclusion

En moins de 10 ans,

- Importance croissante des techniques de médecine régénérative, à base d'injections intra articulaires
- Emergence de l'ingénierie tissulaire
- Véritable alternative à l'utilisation d'AINS, accessibles au bloc opératoire, de façon peu invasive (prise de sang ou lipoaspiration)
- Difficulté des études cliniques prospectives comparatives
- Critères d'évaluation souvent subjectifs
- Nécessité d'évaluations objectives quantifiées : tapis de marche, dosages biochimiques …