Mechanisms of action and role of intra-articular therapy in the management of chronic synovitis

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- Introduction
- Chronic synovitis
  - Normal synovial tissue
  - Main causes of synovitis
- Current therapy
  - Intra-articular Injection
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  - Pharmacokinetics/pharmacodynamics/technical consideration
- Therapies under development
  - New delivery systems
  - New molecules
- Conclusion
INTRODUCTION

- Chronic synovitis → chronic inflammation of the synovial membrane in the joint
- Affect 3% of the western population
- Many causes → rheumatoid arthritis (RA) is the most important
- Several treatments :
  - Systemic treatments : immunosuppressive
  - Intra-articular injections
- Studies to improve these drugs efficiency
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NORMAL SYNOVIAL TISSUE

Articulating bone

Synovial (joint) cavity (contains synovial fluid)

Articulating bone

Synoviocytes

Collagen fiber

Areolar connective tissue

Adipocytes

Synovial membrane (secretes synovial fluid)
NORMAL SYNOVIAL TISSUE

- Synovial membrane 60μm : 2 strates intima & subintima
- In between : subsynovium
NORMAL SYNOVIAL TISSUE

- Trophicity and lubrication → synovial fluid
- Composed by hyaluronic acid, many properties:
  - viscoelastic
  - antalgic
  - anti-inflammatory
  - chondroprotectrices
  - healing

- Synoviocytes:
  - defense against pathogens
  - elimination of intra-articular debris
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RHEUMATOID ARTHRITIS

- Unknown triggering mechanism
- Actors
  - Lymphocytes
  - Macrophages & neutrophils
  - Synovial fibroblasts
- Diagnosis: ACPA, RF

⇒ Synovial hypertrophy and chronic joint inflammation
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INTRA-ARTICULAR INJECTION

- local procedure
- role: to increase treatment efficacy
- avoid infections

- Desinfected anatomical surface
- Ultrasound/X-ray
- Aseptic environment
- Intraarticular Needle
CORTICOSTEROID INJECTIONS

- Injectable corticosteroids: methylprednisolone acetate; triamcinolone acetate etc.

- Clearance preventing methods → 12h half-life
Radionuclide-loaded colloidal particles are rapidly phagocytized by macrophages.

- Size requirement:
  - 2-10 μm

Action

- Genotoxic effect:
  - cutaneous necrosis
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PHARMACODYNAMICS/-KINETICS

- Influencing factors:
  - Dissociation constant
  - Molecular size
  - Protein binding
  - Solubility
  - Inflammation
    - ↑ Capillary permeability
    - ↑ Lymphatic drainage
    - ↓ Proliferated cells decrease uptake

- Half lives NSAIDS and soluble steroids: 1-4 hours
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NANOPARTICLES

- Synthetic polymers: ↑ retention time
- Reach target site → release drugs → degrade
- Release rate and degradation factors:
  - Nanoparticle: composition, molecular weight, crystallinity
  - Drug: nature, size, load
- Research on properties and safety
- Potential: 20x longer retention time
NEW DRUG DELIVERY: ANTIBODIES

- **number MØ → severity of synovitis**
- **Inflammatory MØ express folate receptor β (FRβ) – binds mAb coupled with an immunotoxin**
- **MØ removal → lower grades of inflammation**
- **14 d positive result**
- **No significant systemic effect**
PEG

- PEGylation
- Conjugation of polyethylene glycol
- For hydrophobic and small molecules
- Increase their molecular weight
- Delay systemic elimination
- An example: Corticosteroids
- < 700 Da
- PEGylation to increase the half life
- But rarely exceed 12h
LIPOSOME

- Spherical vesicle
- Coated with PEG = Long circulation “stealth” liposome
- Recognition of targeted cells = Immunoliposome
- Advantages:
  - Increase therapeutic activity
  - Reduce systemic complications
- Some limits...
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TNF-α

- Inflammatory cytokine
  - Inflammatory and immune reactions
    - Neutrophil recruitment
    - VEGF
    - Co-stimulator:
      ★ Tc activation
      ★ Ab production

- Antagonists use to treat auto-immune diseases (RA)
- Clinical studies has been done: positive
- Costs vs. Effectiveness
- Side effects
VEGF

- Study links VEGF expression to IAT failure in RA
- Animal study: blocking VEGF → articular inflammation
- Current pilot: anti-VEGF antibody efficacy in recurrent hemarthroses for hemophilia patients
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CONCLUSION

- Current therapies but not effective for all the patients

- New promising therapies
  - New delivery systems: nanoparticles, antibodies, PEG, liposomes
  - New target molecules: TNFα, VEGF

- More clinical trials need to be done…

- Other approaches: genetic and cell therapies
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Thank you for your attention!