Bone Targeting

Bisphosphonate based Osteotropic Drug Delivery System for metastatic bone treatment by oral route

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INTRODUCTION

Bisphosphonate based Osteotropic Drug Delivery System for metastatic bone treatment by oral route
Many oncology patients with solid tumors get secondary metastases to bone.

Current metastatic bone treatments are bisphosphonates by intravenous route

(WorldWide sales > $1 billion)

→ Unmet medical need for patients treated by regular infusions at hospitals / clinics

as no oral formulation is available
**Bone**: a complex organ responsible for structure, calcium storage and hematopoïesis

**Structure**:
- 50-70% mineral
- 20-40% organic matrix
- 5-10% water
- 1-5% lipids

Main component: hydroxyapatite crystals (HAP)
Bone turn-over: a bone remodeling cycle:

- Osteoblastic bone formation
- Osteoclastic bone resorption
- Mineralization
Alteration of bone’s catabolism and/or anabolism of bone diseases

**Osteoporosis:**
- bone resorption > bone formation

**Other pathologies:**
- osteosarcoma,
- bone metastasis,
- osteoarthritis,
- osteomyelitis...
II Bone Targeting
Characteristics of Bone disease state: INFLAMATION
Enhanced Permeability & Retention (EPR)

Exposure of HAP to blood used to deliver drugs to diseased tissue
Bone seeking agents

Tetracyclines

Mode of action:
Stop Protein elongation
via inhibition of aminoacyl-tRNA

Correct orientation of Tetracycline required to bind to HAP

Research of a minimalized tetracycline structure to reduce side effects and retain capacity to bind to HAP

3-amino-2,6 dihydroxybenzamide
(50% ability to bind to HAP vs tetracycline)
Bone seeking agents

Acidic Oligopeptides

Bone SialoProtein (BSP) : Bone protein with high affinity to HAP

From BSP Acidic, Oligopeptides with 4 to 10 AminoAcids have been designed for enhanced Biocompatibility

Based on Glutamic and Aspartic acids

In vivo trials :
i.v injection into mice of estradiol-17\text{\textbeta }-\text{succinate-}(L-\text{Asp})_{6}

→ 
affinities of AO depend only the number of AA, not on their L or D characters or their species
Bone seeking agents: **BISPHOSPHONATES**

*The most studied bone targeting molecules*

**Mode of action:** binding to the inorganic part of HAP
BISPHOSPHONATES

First biological activity discovered in 1968

- BPs’ strong affinity to HAP:
  - Retained even conjugated to other molecules
  - Relevant in bone scintigraphie

- Use of Tc99 labeled methylene diphosphate (MDP) or hydroxy methylene diphosphate (HDMP)
Advantages of using Bisphosphonates as polymer/nanoparticle targeting moieties

- **Amino BP**: primary amine
  Can be conjugated to carboxylic acids

- **Conjugaison to nanomedecines via a degradable linker**
  Product of synergic effects when coupled with appropriate drugs

+ Soon expiration of BPs’ patent protection → economic option
Bone Targeting using Bisphosphonates

Efficiency demonstrated *in vivo* with targeted osteoprotegerin (OPG) as a model therapeutic protein


**Method:**

Conjugaison of OPG with a « Bone seeking » Thiol Bisphosphonate

*Intravenous administration* in a rat model of osteoarthritis
Results:

Delivery of OPG-thiol-BP to bone:

4 fold / control OPG in osteoarthritis rats

Targeting of control OPG and OPG-thiolBP conjugates to femur and tibia in rats with osteoarthritis.

Significant advantage of BP conjugation as strategy in osteopenic bone diseases.
Bisphosphonates anti-angiogenic properties

most bone metastases are characterized by excess osteoclast number and activity.

Some bisphosphonates, potent inhibitors of osteoclast activity, are widely used for prevention of bone metastases.

Bisphosphonates are also used to treat hypercalcemia of malignancy, osteosarcoma and multiple myeloma.
Bisphosphonates anti-angiogenic properties

**Effects:** apoptosis, inhibition of migration, reduction of angiogenic sprouts of endothelial tissue
OSTEOTROPIC
DRUG DELIVERY SYSTEMS
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A lot have been studied!
OSTEOTROPIC DRUG DELIVERY SYSTEMS

Poly[N-(2-hydroxypropyl)methacrylamide]: HPMA

The most studied polymer therapeutics to bone

*Used in the design of micelles and dendrimers*

Properties:
- Biodistribution to bone
- Bone targeting abilities
- Low toxicity profile

In vivo data

**HPMA copolymer – D-Asp8 conjugate:** Administration i.v of bone-targeted and non-targeted HPMA copolymers into mice

**HPMA copolymer–alendronate (ALN) conjugate**

I.V injection of conjugates with different Mw and ALN content into mice
All Osteotropic Drug Delivery Systems Evaluated *in vivo* to date have been administered *intravenously*

This is why a novel Bisphosphonate Osteotropic Drug Delivery System (*BP-ODDS*) has been developed by INSCB *for ORAL ROUTE* to improve Bisphosphonates oral bioavailability...

...thereby enabling the development of oral dosage forms for oncology indications.
Bisphophonates for cancer therapies are administered *intravenously by slow infusion*.

Infusion of bisphosphonates is however associated with dose and infusion rate dependent effects on renal function.

Oral administration, is complicated by poor bioavailability and poor gastrointestinal tolerability.

This limits their use in oncology to intravenous infusion to achieve the doses required for efficacy.
Bisphosphonates have very poor oral bioavailabilities: 

0.6% in average!

Design of drug delivery systems enhancing oral absorption is required for treatment efficiency!
INSCB proprietary technology combines two factors affecting Bisphosphonates physico-chemical and pharmacological behaviour \textit{in vivo}

Their specific transport through intestinal membrane by paracellular pathway

... Their ability to form insoluble calcium complexes \textit{in vivo} in the GI tract
Two excipients, both registered at pharmacopeias and authorized for oral administration were used to modulate these bisphosphonates properties.

One intestinal penetration enhancer: Sodium Dodecyl Sulfate

One calcium chelatant agent: Myo-Inositol hexakis dihydrogen phosphate dodecasodium
Intestinal penetration enhancement:

Bisphosphonates are highly hydrophilic, they can cross the intestinal membrane only by using the paracellular pathway of intestinal tight junctions.

Sodium Dodecyl sulfate increases intestinal permeability by opening tight junctions, thus enhancing paracellular absorption of Bisphosphonates.
Physiological Calcium chelation
Physiological Calcium chelation

Myo-Inositol is a stronger calcium chelatant than bisphosphonates. Its presence increases bisphosphonate solubility in GI Tract.

→ Bisphosphonates intestinal absorption is enhanced
Manufacturing process

Classical physical dry mixture of excipients and drug substance

Can be processed in a film coated tablet or in hard gelatine capsules.

Technology does not increase manufacturing costs compared to classical tablet or capsule production.

The new formulation shows no degradation of the active drug after one year stability, either in film coated tablet or hard gelatine capsule form.
Comparative Bioavailability study

**Purpose**: To assess relative bioavailability of BP-ODDS, vs reference formulation, a marketed film coated tablet of a bisphosphonate (Actonel 35 mg ®),

**Dose**: 35 mg single dose, administered *per os*, one film-coated tablet of 35 mg with 200 ml of low carbonated water.

**Subjects**: 12 healthy volunteers in fasting conditions

**Selection criteria**: Male & female, aged 18-45, body mass index: 19 - 27.5

**Methodology**: *Two period, two sequence, cross-over, block randomized*

**Duration of treatment**: One day per period

**Pharmacokinetic criteria for evaluation**: Risedronate AUC0-t, Cmax, AUC O-inf, Tmax + (T1/2, MRT).
Comparative Bioavailability study

Comparative Bioavailability of BP-ODDS / INSCB risedronate 35 mg vs marketed Actonel
Comparative Bioavailability study

Interindividual Variability:
CV (%) of Inter Individual concentrations per sampling times by formulation

![Graph showing interindividual variability with CV (%) for Reference Actonel and BP-ODDS/INSCB.](image)
CONCLUSIONS

Statistical analysis of pharmacokinetic data obtained proves that:

Test product: BP-ODDS / INSCB Sodium Risedronate 35 mg, is relevantly better absorbed than reference ACTONEL® 35 mg

AUC of BP-ODDS is almost 300% higher than reference Actonel®

Cmax of BP-ODDS is almost 500% higher than reference Actonel®.

The Bisphosphonate Osteotropic Drug Delivery System (BP-ODDS) developed, is supra-bioavailable when compared to its reference marketed product.
CONCLUSIONS

\( T_{\text{max}} \) of BP-ODDS is half of \( T_{\text{max}} \) of reference Actonel®

\[ \rightarrow \text{twice quicker efficiency for BP-ODDS.} \]

Variability of primary pharmacokinetic parameters of BP-ODDS are lower than variability of reference Actonel®

\( (20\% \text{ lower for } C_{\text{max}} \text{ and } 60\% \text{ lower for } AUC_{0-\text{inf}}) \)

\[ + \text{Safety:} \]

**BP-ODDS administered in single dose, orally, was very well tolerated by the participant subjects.**
BP-ODDS tablets or capsules offer a new paradigm for metastatic bone cancer treatment through the oral route.

Their ability to better target growing metastatic tissues, cover an unmet market need for oral bisphosphonates in oncology.

BP-ODDS is an effective and potentially safer alternative to bisphosphonate intravenous infusions which could offer the following advantages:

* Improved quality of life for the patient
* Cheaper treatment
* Flexibility in the dosing regimen
BP-ODDS could also be used as a carrier for drugs needing vectorization to bone.

Either using the Micelle forming ability of some bisphosphonates to carry the drug candidate:

Or by use of a biodegradable linker to be conjugated to a bisphosphonate or a bisphosphonic group.
This Osteotropic Drug Delivery System has been patented by INSCB in 2011 and is available for license.

Contact: contact@inscb.org
Thanks for your Attention!
APPENDICES
Bone seeking agents

Estradiol analogs

Localisation in bone tissue + lack of estrogenic properties

Methods: Attaching calcium chelators to an estradiol moiety via succinoyl or carboxyethyl linkers

Improvement of targeting potential
2 sorts of Bisphosphonates

**Amino BP**: disturbance of mevalonate pathway
- inhibition of protein prenylation
- and osteoclasts’ loss of function

**Non amino BP**: creation of a modified ATP
- inability to be hydrolysed

**Osteoclasts’ apoptosis and reduced bone turn-over**
Comparative bone seeking properties of Bisphosphonates (BP) Acidic Oligopeptides (AO) and Tetracycline

Rate of binding to HAP: Faster for AO than BP due to a larger binding area of AO

Binding strength: Greater for BP than AO due to a higher specificity of BP for HAP

Binding sites:
- All bone for BP
- Higher crystalline HAP for AO
- Growing surfaces with low crystallinity for Tetracycline
Bone targeting principles

Osteoclast targeting:

Use of BP and AO because of their favored binding onto absorbing surfaces

Osteoblast targeting:

Use of Tetracyclines or analogs because of their favored binding on bone’s growing surfaces
Comparative Bioavailability study

Methodology:

Two period, two sequence, cross-over, block randomized

Hospitalization of subjects: until 24 hours post administration.

Washout period: 46 days.

Blood samplings collected: Before dose (0.0) & 20 sampling points Post dose from 0.25, to 168.0 hours.

Analytical method: Determination of Risedronate in plasma by HPLC- MS/MS.

Comparative bioavailability assessment based on plasma drug levels of test bisphosphonate used, (sodium risedronate).

Safety: Laboratory data / Vital signs / Adverse events
RESULTS: Pharmacokinetics parameters:

Mean pharmacokinetics characteristics of risedronic acid after treatment with REFERENCE: Actonel® and TEST: BP-ODDS / INSCB products.

Comparative bioavailability of the primary parameters (test name: Classic 90% CI):

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUC 0-t</th>
<th>AUC 0-inf</th>
<th>C max</th>
<th>T max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Value</td>
<td>295.854</td>
<td>266.363</td>
<td>480.004</td>
<td>0.530</td>
</tr>
</tbody>
</table>

Comparative coefficients of variation (CV) of the primary pharmacokinetic parameters:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUC 0-t</th>
<th>AUC 0-inf</th>
<th>C max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Value</td>
<td>0.85</td>
<td>0.38</td>
<td>0.79</td>
</tr>
</tbody>
</table>

(CV Test / CV Reference)
Future of the field

Development of bone targeted anti-neoplastic agents
Because bone metastases = unsolved problem in oncology

Research about bone targeted therapeutics focusing on:

- **EPR** effect, Delivery of siRNA to solid tumors
- Combination therapies: (i.e: Paclitaxel / BP; Statins : BP…)
- bone targeting of relevant drugs in order to reduce pain

+ improve quality of life

Continous increase in prevalence of bone diseases with aging population
Many novel drug applications: yet to be explored

Better development of disease specific targeting

Research of bone conditions present in each disease + targeting mechanisms

Discovery of specific biochemical pathways => disease states