Preventing Periodontitis or Controlling its Progression Reduces the Development of Medication-Related Osteonecrosis of the Jaw (MRONJ) in Rice Rats (*Oryzomys Palustris*)

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MRONJ

- Exposed necrotic bone in the oral cavity
  - >8 wk without healing
  - Systemic medications
    - Powerful anti-resorptives [(pARS) eg. Bisphosphonates (Zoledronic acid, ZOL) or anti-RANKL inhibitors]
    - Anti – angiogenics (eg. anti- vascular endothelial growth factors.
  - No history of radiation therapy or apparent metastases to head and neck

- Local oral risk factors
  - Recent tooth extractions
  - Periodontitis (PD), periapical infection
  - Mucosal trauma
Preventative Measures can reduce MRONJ

- Elimination/Reduction of oral and dental risk factors
  - Tooth Extraction
  - Unfitting Removable Denture
  - Peri-implantitis
  - Periodontitis
Preclinical Model of PD and MRONJ

Rice rat (*O. palustris*)

STD rodent chow

**maxillae**

- hard palate
- soft palate

**Food-impaction induced localized PD (FILP) lesions**

**Zoledronic acid (ZOL)**

MRONJ-like lesion

- necrotic bone

60-80% rice rats develop FILP lesions at 16-34 wks of age

Around 94% of FILP lesions occur in the maxilla

(Messer et al 2017)

(Messer et al 2018)
A dietary modification or mechanical dental cleaning in rice rats will prevent or control PD, and hence will reduce the prevalence of MRONJ.

Determine the efficacy of preventing or controlling PD in the development of MRONJ by:

1) Oral mechanical cleaning of Lesions

2) Diet modification
Materials and Methods

**In vivo oral exams under ISO anesthesia (q2wks)**

**SDT diet**
- PD lesions
- n=15/group

**Rice rat (O. Palustris)**

**SF diet**
- High Soluble Fiber (HSF) (7.5% inulin and 10% fructooligosaccharides)
  - No PD lesions
  - n=15/group

**IV q4wks**
- **VEH**
- **ZOL 80μg/Kg**
- **ZOL 80μg/Kg + Dental cleaning (DC)**

**Necropsy**

**OUTCOMES:**
- In vivo analysis of the jaws
- High Resolution Photographs of Jaws (necropsy = 24 wks). Gross Quadrant Grade (GQG)
- MicroCT
- Histopathology
  - decalcified, serially sectioned, and H&E stained
  - Immunohistochemical TRAP staining
In Vivo Analysis of Maxillary Quadrants

- SF+VEH and SF+ZOL rats had significantly lower prevalence of oral lesions than STD rats
- STD+ZOL rats that received dental cleanings had significantly reduced severity of PD lesions.
Ex-Vivo Gross Analysis of Oral Lesions

High Resolution Photographs

3D reconstruction of MicroCT slices
Alveolar Bone Loss

Maxillary ABL M2M3

CEJ-ABC distance (µm)

STD+VEH
STD+ZOL
STD+ZOL+DC
SF+VEH
SF+ZOL

no PD
PD
no PD
PD
no PD
PD
no PD
PD

0
200
400
600
800
1000
1200

STD+VEH no PD
STD+VEH PD
STD+ZOL PD
STD+ZOL+DC PD
SF+VEH no PD
SF+ZOL no PD

M1
M2
M3
CEJ
ABC

500 µm

500 µm
Immunohistochemical staining of TRAP+ Cells

Quantification of osteoclast number/mm²

Immunohistochemical TRAP stained sections. Red arrow indicates TRAP+ osteoclast
Histopathologic Assessment

### Maxillary Histological PD Scores at 24 weeks (M2M3)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PD Score</th>
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<tbody>
<tr>
<td>STD VEH</td>
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<tr>
<td>STD ZOL</td>
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<tr>
<td>STD ZOL+DC</td>
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<tr>
<td>SF VEH</td>
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<td>SF ZOL</td>
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#### Empty Osteocyte Lacunae

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percent</th>
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<tbody>
<tr>
<td>STD+VEH PD</td>
<td></td>
</tr>
<tr>
<td>STD+ZOL</td>
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<tr>
<td>STD+ZOL+DC</td>
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#### MRONJ Prevalence

- Exposed necrotic bone
- Lack of overlying gingival epithelium
- ≥10 confluent empty osteocyte lacunae
Conclusions

• Dental cleaning reduces gross severity and extension but does not resolve PD lesions in rice rats.

• Preventing progression of PD reduces occurrence of MRONJ.

• SF diet prevented the development of PD and MRONJ regardless of treatment.

• These findings provide direct preclinical evidence to support current guidelines concerning maintenance of good oral hygiene in pAR patients.