Update on Clinical Research in Fibrous Dysplasia/McCune-Albright Syndrome

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NIDCR, NIH
FD Foundation Patient and Family Conference 2017
RANKL Regulates Bone Resorbing Cells

Osteoclast Precursor

RANK

RANKL

bone cell

differentiation and fusion of osteoclast precursors

Activated Osteoclast

BONE Modeling & Remodeling
FD Cells Produce High Levels of RANKL *in vitro*
RANKL is highly expressed in proliferative FD
Denosumab
(Xgeva™)

- Humanized monoclonal antibody to RANKL

- FDA-Approved treatment in adults:
  - Prevention of skeletal-related events from bone metastases from solid tumors
  - Giant cell tumors of the bone

- Approved treatment in adolescents (skeletally mature):
  - Giant cell tumors of the bone
RANKL Regulates Bone Resorbing Cells

- Differentiation and fusion of osteoclast precursors
- Osteoclast Precursor
- DMAB = denosumab
- BONE Modeling & Remodeling
Compassionate use study of denosumab for FD

Concerning side effects

Boyce, JBMR, 2012
Denosumab - Growth Plate Effects

Wang, JCEM, 2014
Denosumab and Post-Treatment Rebound

- Ten additional cases of hypercalcemia
  - 9 kids: Giant cell tumor, Juvenile Paget’s disease, fibrous dysplasia
  - 1 adult
- Vertebral fractures after discontinuation: emerging cases
Pilot Study of safety and efficacy of Denosumab to treat FD: T-D-0041

**on-drug phase**

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D = denosumab dose

**off-drug phase**

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**End points:** bone turnover, pain relief, lesion size (\(^{18}\)F-sodium fluoride PET/CT bone scan), biopsies (histomorphometry, Ki67 index), safety (calcium and phosphate)

**Status:** IRB-approved, Amgen support pending, projected start date fall 2017
Interleukin-6 (IL-6): inflammatory cytokine

- Role in wound healing, infections, trauma
- FD cells produce IL-6 \textit{in vitro}
- Role of inflammation in FD
Tocilizumab

• IL-6 inhibitor
• Used for rheumatoid arthritis, inflammatory disorders
• Case reports of improved FD pain
• Placebo-controlled trial in Lyon, France ongoing
Creating an International Consortium

• Masterclass in Oxford October 2015, planned by:
  – FD Support Society UK
  – Oxford Musculoskeletal Research Unit
  – NIHR Musculoskeletal Rare Diseases Translational Research Collaboration

• Attendees:
  – Clinicians and researchers from NIH, Leiden, Turin, Lyon, Florence & Oxford
  – Representatives from UK and US-based patient advocacy groups
Oxford Masterclass in Fibrous Dysplasia

Day 1: Patients
- Support & networking
- Healthcare access
- Q&A with clinicians

Day 2: Patients + Clinicians / Researchers
- Review ongoing research activities
- Identify unmet needs, research priorities

Day 3: Clinicians / Researchers
- Case presentations
- Collaborative research
- International clinical care guidelines

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Improving patient outcomes in fibrous dysplasia/McCune-Albright syndrome: an international multidisciplinary workshop to inform an international partnership.

Boyce AM1,2,3, Turner A4, Watts L4, Forestier-Zhang L4, Underhill A5, Pinedo-Villanueva R4, Monsell F6, Tessaris D7, Burren C6, Masi L9, Hamdy N9, Brandi ML8, Chapurial R10, Collins MT1, Javadi MK11.
Second International Meeting

- November 2016 in Lyon, France
- Attendees: Clinician/researchers & patient advocacy reps from US, UK, France, Italy
- Outcomes
  - Consensus on diagnostic criteria for FD/MAS
  - Draft outline for international clinical care guidelines
Development of International Clinical Care Guidelines for FD/MAS: Modified Delphi Consensus Approach

1\textsuperscript{st} International Meeting 10/2015: Identified need for global harmonization in care

2\textsuperscript{nd} International Meeting 11/2016: Draft outline created

3\textsuperscript{rd} International Meeting 11/2017: Anticipated finalization of guidelines

12/2016-present: Draft circulated to wider of group of 52 clinicians, researchers & advocates from Europe, Americas & Asia
Other Ongoing Activities

• Working network of advocacy groups formed from US, UK, Italy, France, & Netherlands

Increased Risk of Breast Cancer at a Young Age in Women with Fibrous Dysplasia.

Majoor BC1, Boyce AM2, Bovée Jv3, Smit VT3, Collins MT2, Cleton-Jansen AM3, Dekkers OM4,5,6, Handy NA4, Dijkstra PS1, Appelman-Dijkstra NM4.

Possible Increased Risk of Breast Cancer in FD/MAS Patients

09.01.17

Researchers from Leiden University Medical Center (LUMC) in the Netherlands and the National Institutes of Health (NIH) in the US have recently concluded a study researching the link between breast cancer and fibrous dysplasia and McCune-Albright syndrome (FD/MAS). Their findings suggest that FD/MAS patients may be more likely to develop breast cancer, and at a younger age, than the general population.
Future Activities

• 3rd meeting Leiden Nov 2017
• Goals to:
  – Expand global representation
  – Finalize clinical care guidelines / strategize dissemination
  – Engage additional stakeholders; translational investigators / pharmaceutical industry representatives
  – Strategize harmonizing natural history data between international centers
  – Plan for international clinical trials
Questions?