Welcome!

FLS Bone Health ECHO® TeleECHO Clinic

We will be recording this TeleECHO Clinic for educational and quality improvement purposes.

By participating in this clinic you are consenting to be recorded.

- If you do not wish to be recorded, please email andrea.medeiros@nof.org at least one week prior to the TeleECHO Clinic you wish to attend.
- Please type in your name, location, and email address in the chat.

Some helpful tips:

- Please mute your microphone when not speaking
- Position webcam effectively
- Communicate clearly during clinic:
  - Speak clearly
  - Use chat function

Project ECHO's goal is to protect patient privacy

To help Project ECHO accomplish that goal, please only display or say information that doesn't identify a patient or that cannot be linked to a patient.

References:

For a complete list of protected information under HIPAA, please visit www.hipaa.com

Common HIPAA Identifier Slip-Ups and Easy Ways to Protect Patient Privacy

- 1st – **Names:** Please do not refer to a patient's *first/middle/last name* or use any *initials*, etc. Instead please use the *ECHO ID*.
- 2nd – **Locations:** Please do not identify a patient's *county, city or town*. Instead please use only the patient's *state* if you must or the *ECHO ID*.
- 3rd – **Dates:** Please do not use any dates (like *birthdates*, etc.) that are linked to a patient. Instead please use only the patient's *age* (unless > 89)
- 4th – **Employment:** Please do not identify a patient's *employer*, work *location* or *occupation*. Instead please use the *ECHO ID*.
- 5th – **Other Common Identifiers:** Do not identify patient's *family* members, *friends, co-workers, numbers, e-mails*, etc.

FLS and Hypophosphatasia

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1-9-2019

Improving People's Lives
through innovations in personalized health care

Wexner Medical Center

Disclosures

- Advisor/Review Member: Alexion Pharmaceuticals
- Grant/Research Support: Alexion Pharmaceuticals

Objectives

- Review hypophosphatasia
- Identify hypophosphatasia in adults

Case: sacral stress fracture in 47 y.o woman

- 2013 cc: pain in low back, upper buttock, radiates to L hip, L thigh, sharp, intermittent, worse with walking/standing
- 8/2014 saw PM&R: MRI abnormal signal left sacral ala medial to SI joint suspicious for an osseous lesion either a primary secondary neoplasm…"
- 10/2014 saw Ortho-oncologist: 11/2014 MRI: "improvement in signal abnormality … Overall findings favor resolving stress fracture. "
- 4/2019 pain improving with NSAID and time; endocrinology referral to "evaluate and treat for bone mineral loss"

Case (Cont'd)

- PMH/PSH: acute pancreatitis 2011, s/p cholecystectomy
- FamHx: breast cancer mother, maternal aunt
- SocHx: nonsmoker, wine rarely
- Med: pregabalin, cyclobenzaprine, ibuprofen, acetaminophen
- 5' 4", 133 lbs
- Dentition intact
- No tenderness in back, sacrum, gluteal area
- Normal range of motion lumbar, hip
- +Pelvic tilt

Evaluations

DXA 7/2015		
Region	T-score	Z-score
L-Spine	-1.2	-0.8
LFN	-1.7	-0.9
LTH	-1.4	-0.9
RFN	-1.5	-0.7
RTH	-0.9	-0.8

Tests 6/2015	Result	Ref
Ca	9.9	8.6-10.5
Alb	4.6	3.5-5.0
Phos	3.2	2.2-4.6
Mg	2.0	1.6-2.6
Cr	0.64	0.50-1.20
PTH	27.6	14.0-76.0
25OHD	22.4	30.0-100.0
CTX	277	40-465
BSAP	9.8	5.0-18.2
SPEP/UPEP	Neg	
24hr U-Ca	161	100-300
TSH	1.296	

Test	Result	Reference
ALP	33	32-126 U/L
Vitamin B6	29.5	2.1-21.7 ng/ml
U-PEA	53	<48 noml/mg Cr
ALP	31	32-126 U/L
ALP (outside)	30, 36, 29, 28, 31, 37	40-150 U/L

4/2016 Medical Genetics; *ALPL* mutation analysis: +heterozygous c.407G>A (p.R136H) ***pathogenic variant*** in exon 5 of the *ALPL* gene. The c.407G>A is a missense mutation substituting arginine for histidine at codon 407. This c.407G>A mutation has been previously reported in the literature as a pathogenetic variant in a 3 year-old patient who was a compound heterozygote for mutations in the *ALPL* gene and was affected at a young age. There is one publication of an in vitro study which suggests this variant is a mild allele.

Further History

- No h/o rickets, premature loss of deciduous teeth
- Mother s/p full dental extraction, dentures in her 20s
- 30 y.o. daughter had 5 dental extractions, 5 more to pull, and other teeth that need fillings
- Elementary school: achy pain in bilat arm/legs
- Generalized muscle aches and pains
- “I have tight muscles and pain all over the body”
- Since 20s: bilateral achy shin pain, every few months, last days
- Foot pain episodes
- 2012 Tried to start jogging, unable due to back pain
- 10/2018 Left knee pain, x-ray medial compartment chondrocalcinosis, ? CPPD

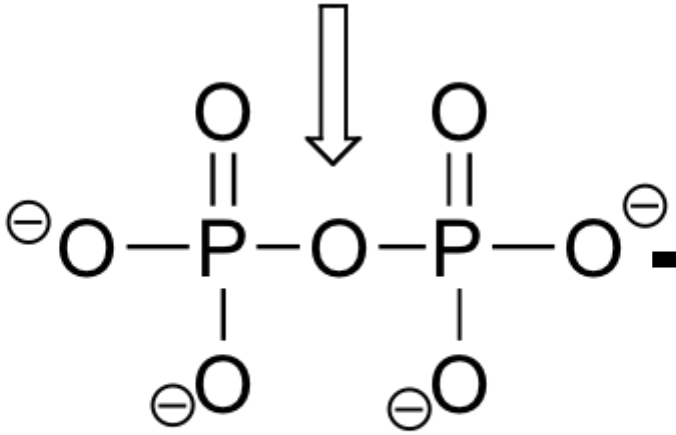
Case

- Sacral stress fracture: recurrent, slow to heal
- Intermittent pain
  - Uses cane with increased activity, prevents sacral pain
  - F/U MRI showed worsened signal L sacrum, ilium
- Pain exacerbated by
  - Lifting food at a food pantry/food bank
  - Mildly vigorous exercises: leg lifts, sit-ups, jogging
  - Limits activities

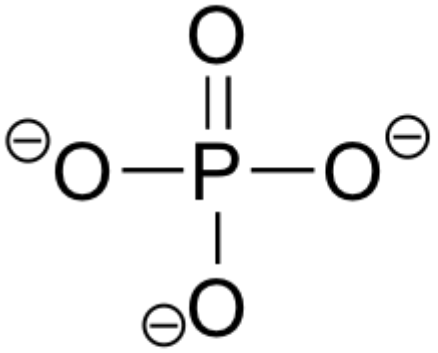
Hypophosphatasia (HPP)

- Inherited, lifelong condition affecting bones, teeth
- Ultra-rare (< 20 per million)
- Defective tissue nonspecific alkaline phosphatase (ALP)
- Hallmark blood test: Low ALP levels
- ALP dephosphorylates substrates
  - pyrophosphate (PPi), pyridoxal-5'-phosphate
- PPi inhibits hydroxyapatate formation
- Unmineralized osteoid accumulation
- Rickets, osteomalacia

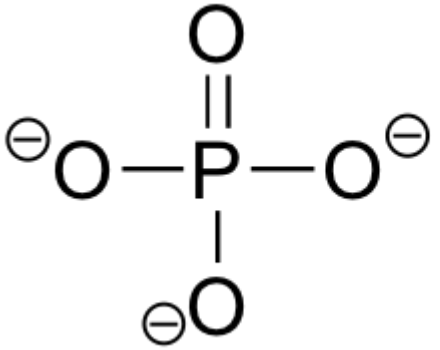
Pyrophosphate (PPi)



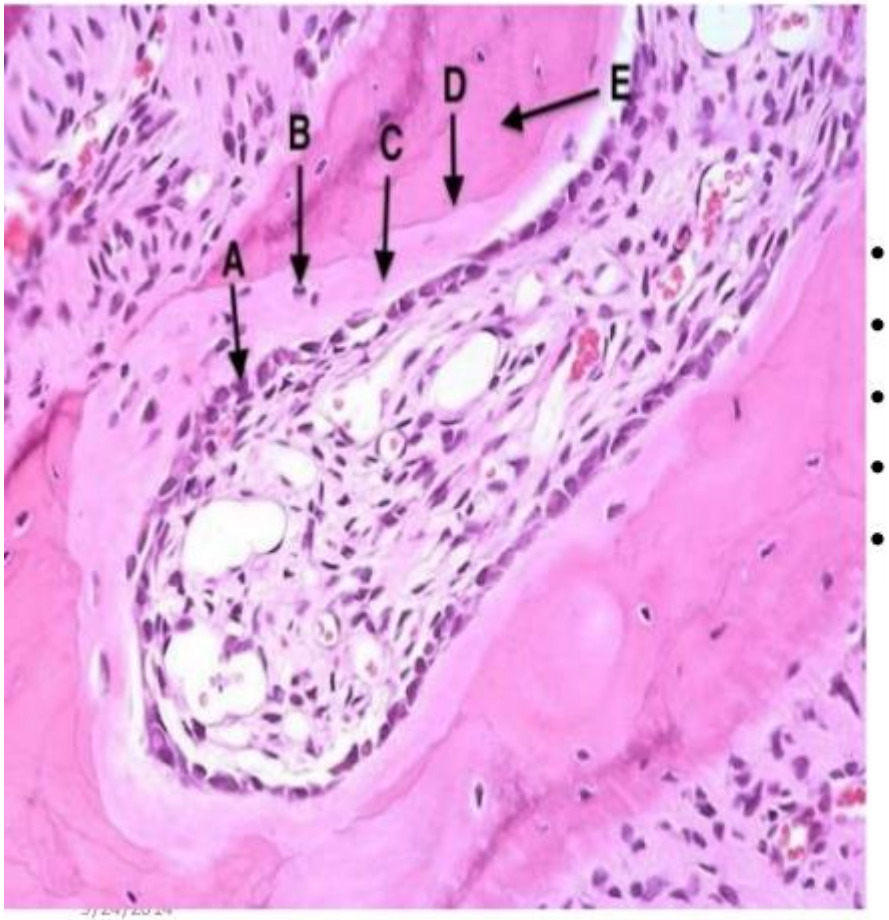
inorganic pyrophosphate (PP_i)



inorganic phosphate (P_i)



Osteomalacia



- A = osteoblasts,
- B = osteocytes,
- C = osteoid,
- D = cement line
- E = bone

HPP Classification

- Perinatal – Infantile – Juvenile – Adult – Odonto

  <6M 6M-18Y >18Y

  More Severe ←----------→ Less Severe

- Variable presentations in adults
  - Ped-onset sx → continue thru adulthood
  - Ped-onset sx → resolves & recur in adulthood
  - Odonto-only
  - Adult-only

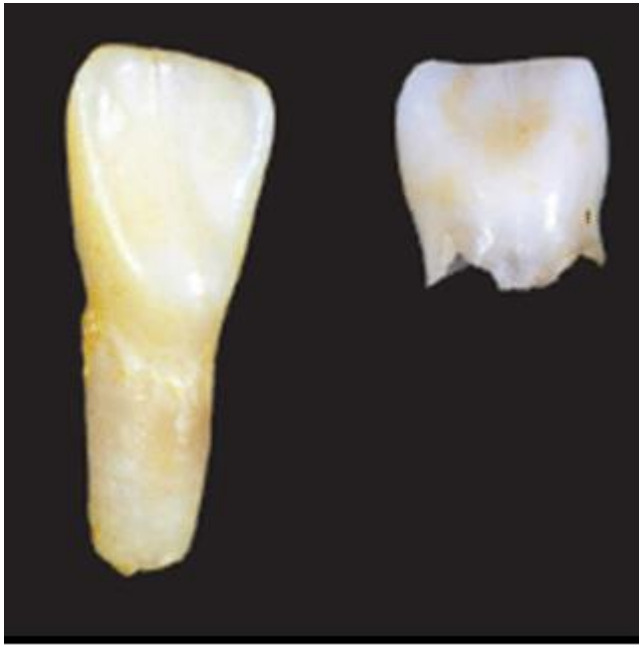
Wexner Medical Center

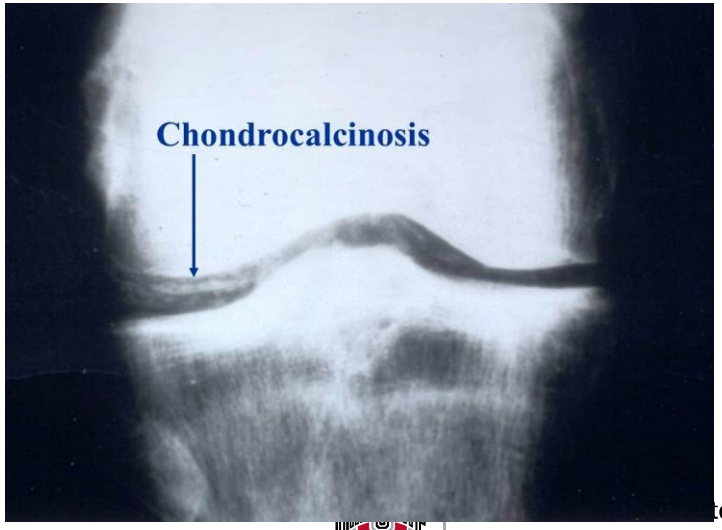
Manifestations of HPP

- Skeleton:
  - Demineralized bones (osteomalacia)
  - Bowed legs (rickets)
  - Recurrent fractures, nonhealing fractures
  - Bone Pain
  - Shorter stature

Manifestations (Cont'd)

- Respiratory:
  - Respiratory failure
- Neurologic:
  - Seizures
- Muscular:
  - Muscle weakness
  - Gait problems
- Dental
  - Early loss of deciduous teeth
- Joint:
  - Chondrocalcinosis, pseudogout
- Kidney
  - Calcifications





Adult-onset HPP Manifestations

Musculoskeletal pain

Metatarsal fractures

Femoral pseudofractures

Early loss of adult teeth

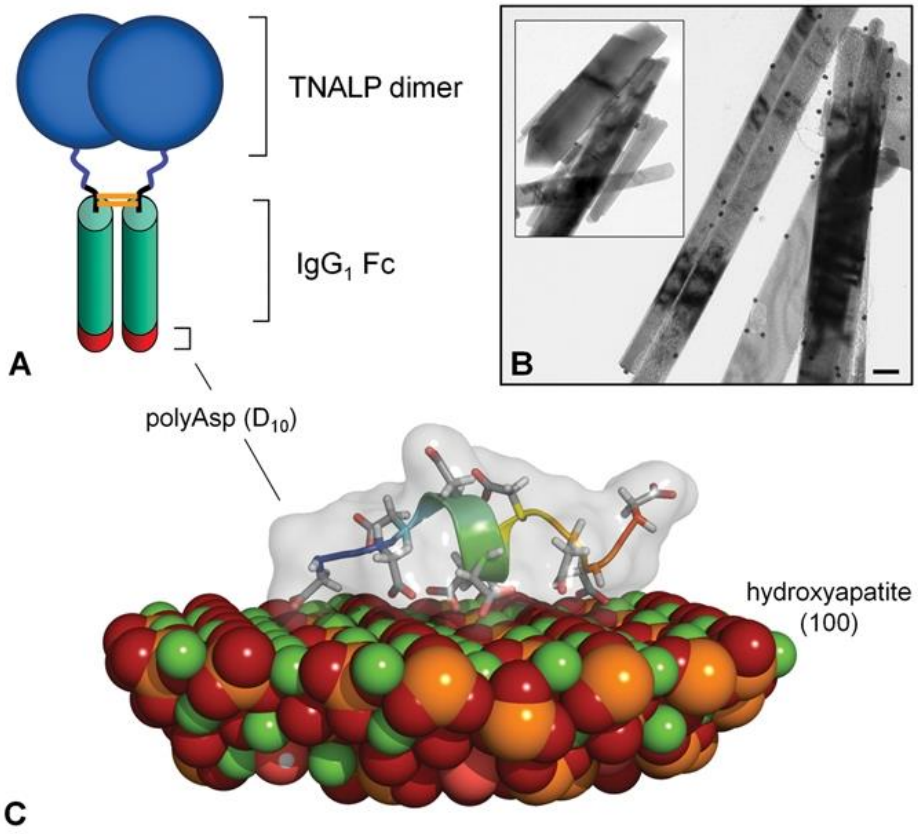
Limited mobility/myopathy

Cartilage calcifications

Pseudogout

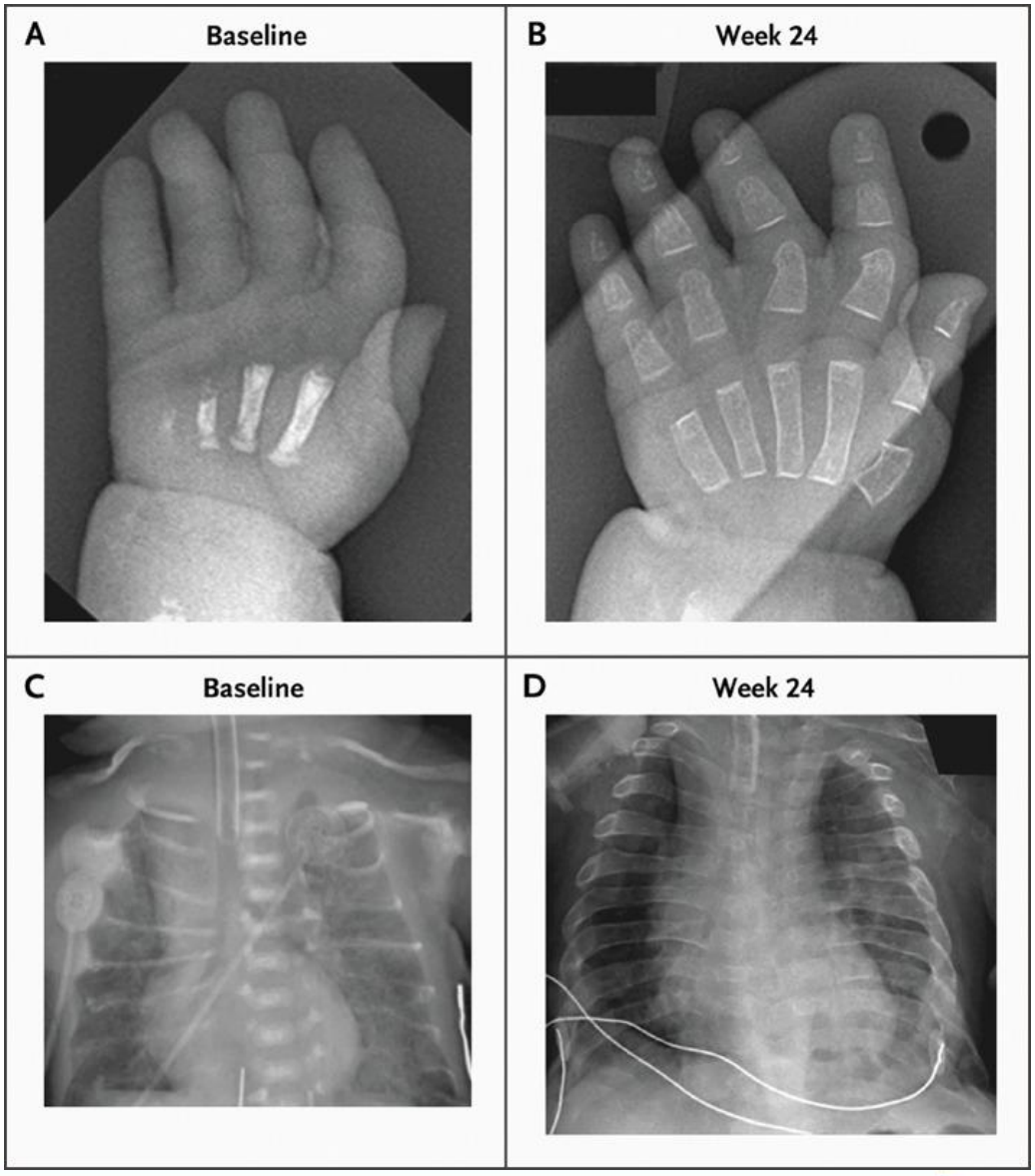
HPP Therapy: asfotase alfa

Bone-Targeted Enzyme Replacement



McKee, M.D., et al. J Dent Res, 2011;**90**(4):470-6

FDA Approval of Asofotase Alfa

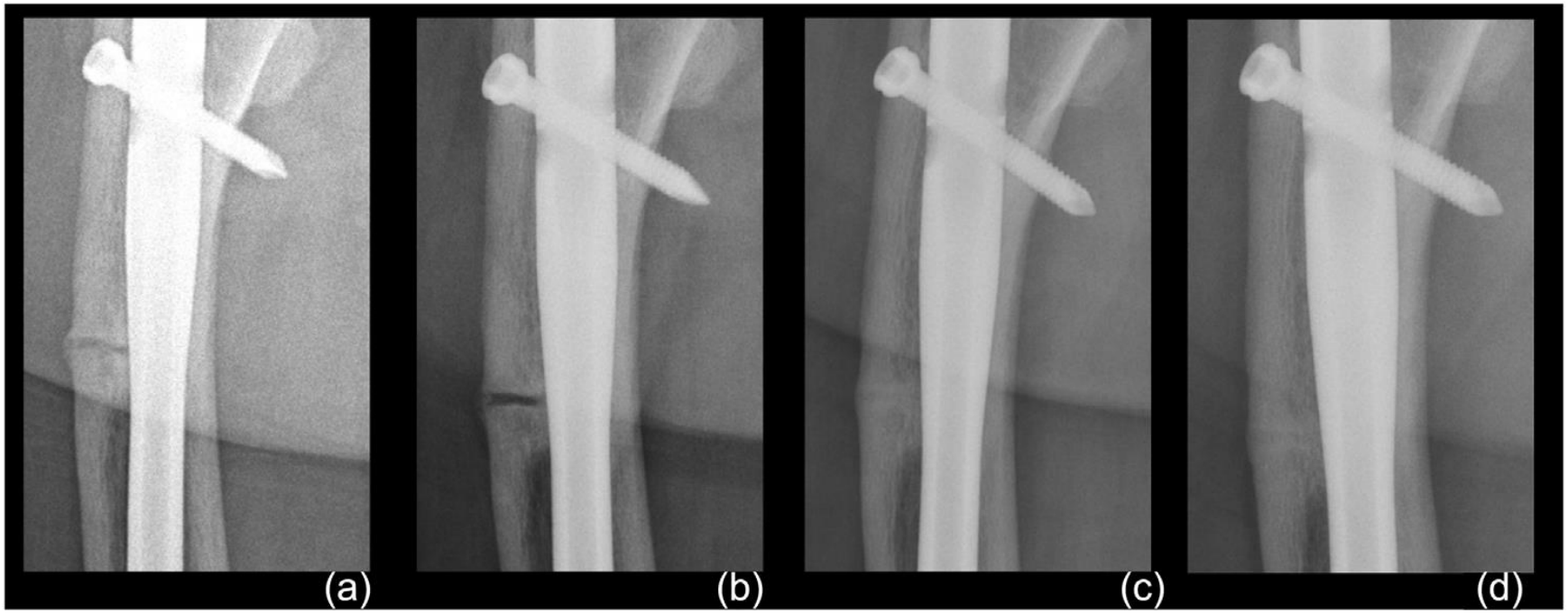


10/2015 FDA approves asofotase alfa (Strensiq™)

HPP: Perinatal-onset
Infantile-onset
Juvenile-onset

Whyte et. al NEJM 2012; 366:904-913

Asfotase alfa & Fracture Healing in HPP

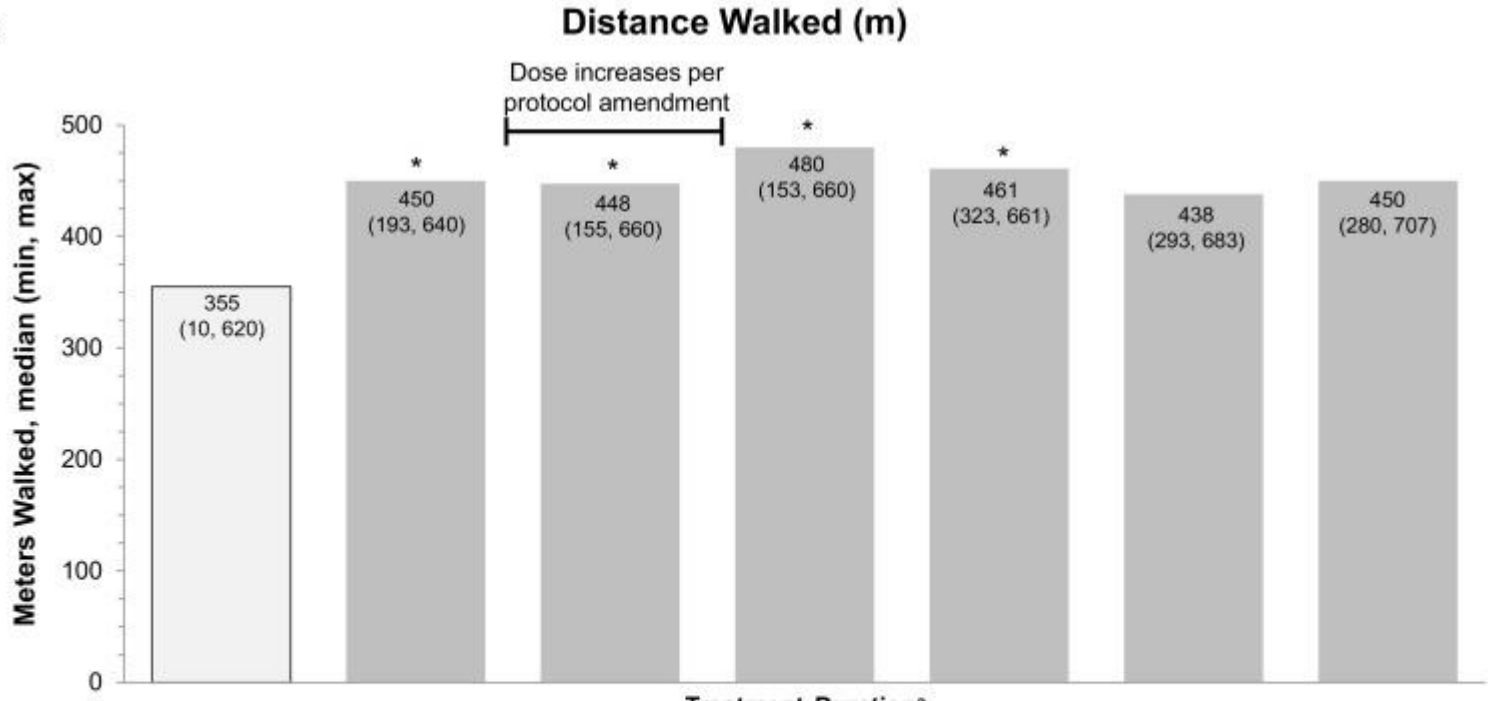


12 Y after fxr 5 Y before Tx	17 Y after fxr 1 M before Tx	11 M after asfotase alfa	14 M after asfotase alfa

Ing et. al. JBMR Plus 2018;2(5):3014-7

Asfotase alfa in adults and adolescents

a



	Baseline	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
	n=19	n=17	n=18	n=17	n=14	n=14	n=13
Mean (SD)	352 (189)	455 (128)	433 (146)	459 (149)	476 (106)	453 (123)	460 (140)
Change from Baseline:							
Mean (95% CI)		65 (34, 96)	62 (23, 100)	67 (28, 105)	78 (35, 122)	50 (–21, 122)	43 (–27, 113)
Median (min, max)		40 (–2, 182)	49 (–123, 197)	69 (–70, 217)	83 (–45, 218)	61 (–187, 240)	67 (–213, 239)

Kishnani, Bone 2019;121:149-62

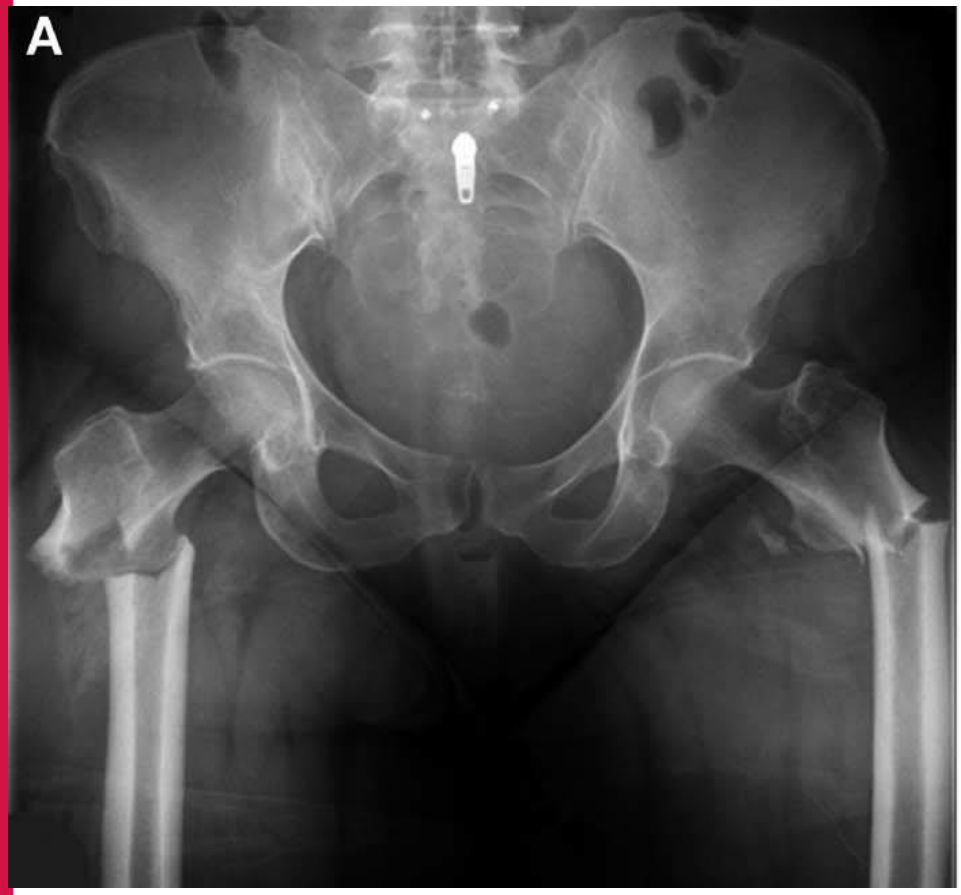
Asfotase alfa in adults and adolescents

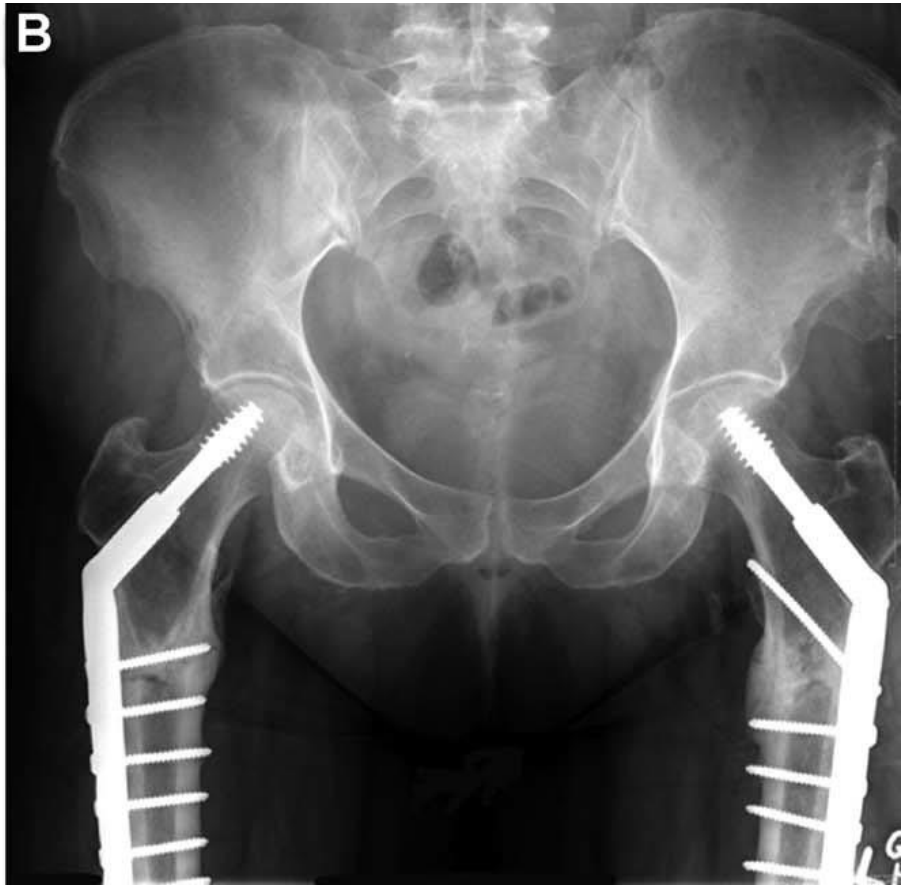
- At baseline, 5 of 19 used gait-assistive device
- By year 2 all 5 improved
  - 1 wheelchair → crutches
  - 1 walker→ cane
  - 1 wheeled walker → independent
  - 2 cane → independent

Kishnani, Bone 2019;121:149-62

AFF During Bisphosphonate Tx in Adult HPP

- LS T-score -2.5 → ALN x 3 years → ZOL x 2
- ALP <25 and 26 (42-116), recurrent metatarsal fractures on bisphosphonate
- While standing at work, collapsed to floor, +heterozogous c.212G>A, p.Arg71His





Sutton, JBMR 2012;27(5):987-4

Phase 4 Study: REBUILD

- Phase 4, randomized, multicenter, Open-Label, 2-Dosage Regimen, safety and tolerability, efficacy, PK/PD study of asfotase alfa in adult patients with pediatric-onset HPP
- Pediatric-onset HPP based on signs and symptoms consistent with HPP
- ≥ 1 nonvertebral fracture (or pseudofracture) incurred without evidence of significant trauma.
- Current unhealed fracture or lower extremity pseudofracture (femoral, tibial, fibular, metatarsal) ≥3 months

https://clinicaltrials.gov/ct2/show/NCT04189315?cond=Hypophosphatasia&draw=2&rank=1
Accessed 1/3/2016

Take-home Points

- Consider HPP diagnosis
  - Low ALP levels
  - Lowish ALP after fracture
- Avoid anti-resorptive agents in HPP
- Measuring vitamin B6 (PLP) may help in acute fracture setting


2020
Happy · New · Year