Response to pamidronate therapy and pharmacogenetics in patients with Osteogenesis Imperfecta.

Nalini MS[1] , Janet YH Hong[1], Nadiah MN[2], Nor Azian AM[2], Syed Zulkifli SZ[3], Zarina AL[3] ,Bilkis Banu AA [3], Fuziah MZ[1], Rahmah R[3]
1.Department of Pediatrics, Hospital Putrajaya, Jalan P9, present 7, 62250 Putrajaya, Malaysia, 2. UKM Medical Molecular Biology Institute (UMBI), Jalan Yaacob Latif, Bandar Tun Razak, Cheras, Kuala Lumpur, Malaysia 3. Department of Pediatrics, UKM Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, Cheras, Kualalumpur, Malaysia

INTRODUCTION

- Osteogenesis Imperfecta (OI), is a genetically heterogeneous connective tissue disorder associated with skeletal fragility, deformity, and growth deficiency.
- Intravenous bisphosphonate therapy is the mainstay of medical treatment of this condition.

OBJECTIVES

- To identify the relationship between genotype and phenotype of patients with OI.
- To evaluate the effects of pamidronate on fracture incidence and growth.
- To evaluate the pharmacogenetic effects of bisphosphonate therapy.

METHODS

- Genetic analysis was performed in 29 children with OI [Type I n = 4, Type III n = 16, Type IV n = 4 and Type V n = 3) from the UKM Medical Centre (UKMMC) and Putrajaya Hospital, Malaysia. 25 patients were on pamidronate treatment.
- Srudy period : November 2013 – June 2017
- Clinical, biochemical and radiological data was collected prior to and at several times during treatment.
- Targeted sequencing of genes was performed using the Ion AmpliSeq in the Ion Torrent™ semiconductor sequencer to identify the mutations. The identified mutations were validated using Sanger sequencing and *in silico* analysis was performed to evaluate the effects of the candidate mutations at protein level.

RESULTS

1.Baseline Characteristics

Table 1
Clinical Characteristics by OI Type

	OI I	OI III	OI IV	OI V	Patient group
No (%)	5 (17.2)	16 (55.2)	5 (17.2)	3 (10.3)	29
Gender (F/M)	1/4	8/8	2/3	2/1	13/16
Blue sclera (%)	5	16	5	3	29 (100)
Dentinogenesis Imperfecta	2	15	3	3	23
Hearing Loss	1	3	1	0	5
Bone deformity	1	16	5	3	25
Mean age of starting treatment (yrs)*	6.9	4.3 +/- 4	5.3 +/- 2.7	8.8 +/- 5.5	6.2 +/- 3.8
Fracture rate prior to starting treatment*	0.15	3.1 +/- 1.5	0.7 +/- 0.2	2.2 +/- 0.3	2.0 +/- 1.4
Treatment length (yrs)*	4.2	5.7 +/- 3.2	5.0 +/- 3.4	6.6 +/- 4.0	5.6 +/- 3.1

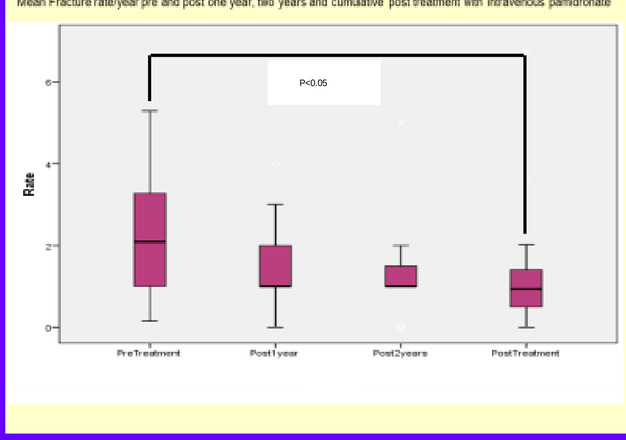
Table 2
Mutational Analysis of patients

Mutations	Number (%)
COL1A1	14 (48.3)
COL1A2	4 (13.8)
IFITM5	3 (10.3)
P3H1	3 (10.3)
SERPINF1	1(3.5)
BMP1	1(3.5)
No mutations	3 (10.3)

2. Response to Pamidronate therapy

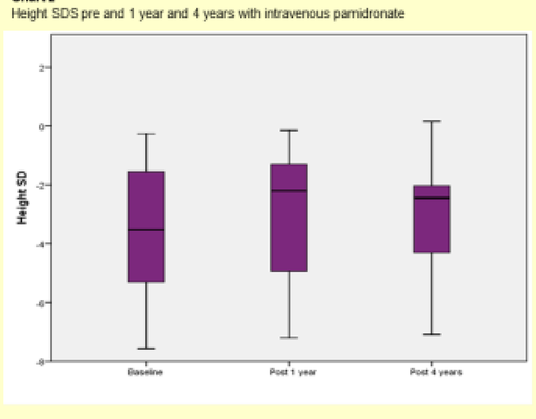
2.1 Fracture Rate

Chart 1
Mean Fracture rate/year pre and post one year, two years and cumulative post treatment with intravenous pamidronate



2.2 Height SD

Chart 2
Height SDS pre and 1 year and 4 years with intravenous pamidronate



3. Pharmacogenetic effects of pamidronate therapy

Table 3
Relationship between clinical characteristics and types of mutation

Characteristics	Quantitative mutation (n = 6)	Qualitative mutation (n = 12)	p value
OI Type (I/III/IV)	5/0/1	0/11/4	< 0.05
COL1A1/COL1A2	6/0	8/4	0.245
Blue sclera	33.3%	66.7%	
Dentinogenesis Imperfecta	28.6%	71.4%	0.569
Hearing loss	100%	0%	0.33
Bone deformity	0%	100%	<0.001
Walk with aid	0%	33.3%	0.245
Treatment	50%	100%	< 0.05

Table 4
Fractures in relation to type of mutation (collagenous genes vs noncollagenous genes)

	No	Δ Fracture (post 1 year – pretreatment)	Δ Fracture (post 2 year – pretreatment)	Δ Fracture (cumulative post treatment – pretreatment)
Collagenous genes	17	0.01	-0.94	-0.77
Non collagenous genes	7	-1.00	-1.00	-1.57
P value		0.089	0.37	0.21

Table 5
Height SD and fractures in relation to type of mutation (COL1A1 vs COL1A2)

	No	Δ Fracture (post 1 year – pretreatment)	Δ Fracture (post 2 year – pretreatment)	Δ Fracture (cumulative post treatment – pretreatment)	Height SD (post 4 years treatment – baseline)
COL1A1	14	0.04	-0.56	0.61	0.61
COL1A2	4	-0.37	-0.87	-0.88	0.07
p value		0.68	0.83	0.67	0.87

- Majority of our patients (55.2%) were OI type III, followed by types I and IV (17.2% each). 73% of our patients had a mutation in the collagen gene.

Response to pamidronate therapy

- The fracture rate decreased at all available time points for patients on pamidronate, compared to the year prior to treatment ***. (Chart 1)***
- There was no significance difference of height pre and post pamidronate therapy. There was no deterioration of height SDS with time among these group of patients***. (Chart 2)***

Pharmacogenetic effects of bisphosphonate treatment

- Patients who had quantitative mutations had a milder phenotype as compared to those with qualitative mutations
- There was no significant difference when comparing individuals who are COL1A1 positive with those who are COL1A2 positive as regard to fracture rate and height SD

CONCLUSIONS

- Patients with haploinsufficiency mutations had a milder phenotype as compared to those with qualitative mutations.
- In the group of patients with helical mutations, the type of alpha chain affected did not influence the fracture rate.
- Cyclic pamidronate administration reduced the fracture rate effectively in patients with OI.

References

1. Lindahl, K., et al., *Genetic epidemiology, prevalence, and genotype-phenotype correlations in the Swedish population with osteogenesis imperfecta.* Eur J Hum Genet, 2015. **23**(8): p. 1042-50.
2. Lin, H.Y., et al., *Genotype and phenotype analysis of Taiwanese patients with osteogenesis imperfecta.* Orphanet J Rare Dis, 2015. **10**: p. 152