Therapeutic options to improve bone health outcomes in Duchenne Muscular Dystrophy – Zoledronic acid and pubertal induction

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Letter to editor:

Dear Editor,

We report outcomes of nine corticosteroid-dependent boys with Duchenne Muscular Dystrophy (DMD), aged d18 years, treated in the last 10 years at The Royal Children's Hospital (RCH), Melbourne with at least one dose of Zoledronic acid (ZA) for vertebral crush fracture (VCF) (defined using Gennant criteria, with loss of >25% anterior and/or middle and/or posterior vertebral height) and with pubertal induction where indicated. Long-term oral corticosteroid therapy used in DMD causes inevitable, progressive bone loss and increased fracture risk,[1-2] with 20-50% of affected boys ambulant prior to fracture losing ability to walk after the fracture.[3] Limited data exist on use of ZA in DMD, with only one published study to date examining its efficacy in vertebral fractures in DMD.[4]

All patients presented were Caucasian and treated with 0.75mg/kg daily prednisolone (n=4), or 0.9mg/kg daily deflazacort (n=5). All ZA infusions were administered at RCH using dosing schedule of 0.04mg/kg 4 monthly. Pubertal induction with oral testosterone undecanoate 40 mg/day, increasing slowly to 120mg/day, was undertaken for boys >14.5 years who had not commenced natural puberty.

Boys ranged from ages 9-14.6 years (SD 1.94) and standing heights of 123-143cm (SD 7.9) at baseline. Annualized bone mineral density increases were all >1%, range 1.20 - 32.30% (SD 9.68) (Table 1). Five of the six patients with interpretable spinal x-rays showed improvement in VCFs with treatment, especially patient 2 who had marked improvement T6 and L2 after 4 doses of ZA. Patients 5, 6, and 8 had no additional fractures and no progression of existing lumbar spine crush fractures after ZA commencement. Functional

mobility was measured using the North Star Ambulatory Assessment (NSAA) in ambulant patients (2, 5, 7, 8, 9), and the Egen Klassifikation in non-ambulant subjects (1, 3, 4, 6). Functional measures were not able to be assessed for patients 4, 5 and 8 as they progressed to non-ambulant during treatment. Patients 1, 2, 3 and 7 demonstrated stable functional mobility over the treatment period; changes in scores from baseline and post-therapy of -3%, 0%, +20% and -8.8% respectively. Patient 6 had a change of -16.7% and patient 9 showed a change of -41% in NSAA but remains ambulant post ZA, at age 15.

No serious adverse events or long bone fractures were documented in this cohort. All patients stated back pain became negligible after ZA commencement.

The case series provides further evidence that use of ZA alongside maintenance of puberty, can stabilise existing VCFs, improve vertebral morphology and maintain mobility status in corticosteroid-dependent DMD boys.

References:

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Table 1. Demographics and pre- and post- treatment characteristics and BMD clinical changes

Clinical parameter baseline and follow-up	Patient number								
	1	2	3	4	5	6	7	8	9
Clinical information									
Duration of steroid therapy before treatment (rounded to nearest year)	6	9	8	8	7	8	3	8	4
Steroid use	Deflazacort	Deflazacort	Prednisolone	Prednisolone	Deflazacort	Prednisolone	Prednisolone	Deflazacort	Deflazacort
Induction of puberty during ZA therapy	Yes	No	No	Yes	No	Yes	No	No	Yes
Age (years rounded down) at beginning of treatment	14	12	14	15	9	15	11	11	12

Baseline height z-score*	-2.50	-3.96	-2.69	-4.33	-2.81	-4.21	-1.84	-2.28	-1.79
Baseline weight z-score*	1.24	0.74	1.66	-1.06	0.35	n/a	1.80	n/a	0.90
Baseline body mass index z-score*	2.29	2.39	2.52	1.73	1.84	n/a	2.43	n/a	1.92
Baseline 25-hydroxy vitamin D level (nmol/L)	58	50	72	45	105	33	64	44	82
Regular vitamin D supplementation[+]	No	No	1000IU daily	1000IU daily	No	No	No	No	1000IU daily
ZA therapy									
Duration of ZA therapy (rounded to nearest 6 months)	1 year	1 year	1 year	1 year	5 years	3 years	2 years	2 years	5 years

No. of doses of ZA	3	4	2	2	10	6	6	5	9
Cumulative average dose per year (mg/kg)	0.12	0.12	0.08	0.08	0.08	0.08	0.12	0.10	0.072
Change in BMD between first- and last- dose of ZA therapy									
Change in LS raw BMD (%)	27.2	1.2	23.4	32.3	11.9	17.9	13.5	9.2	22.0
Change in LS BMD Z-score	-0.19	-0.27	0.30	0.54	-0.01	-1.15	-0.50	-0.61	-0.94
Change in LS BMAD Z-score[a]	-0.07	0.36	1.45	0.52	1.00	-0.83	0.88	0.66	0.51
Baseline LS BMD Z-score prior to ZA therapy	-3.72	-2.64	-4.18	-4.41	-1.14	-4.53	-1.59	-2.02	-0.22
Baseline LS BMAD Z-score[a]	-1.98	-0.41	-2.30	-1.58	0.27	-1.62	-0.71	-0.86	0.70

prior to ZA therapy									

*Values taken from the Centre for Disease Control and Prevention growth chart accessed on 23/05/2017

[+]All patients with a vitamin D level of <50nmmol/L are supplemented with 150,000IU of cholecalciferol until levels reach >50nmmol/L before commencing ZA therapy

[a] BMAD scores taken from the National Institute for Health Bone Mineral Density Z-score Calculator accessed on 23/05/2017

BMAD: Height adjusted bone mineral density; BMD: Bone mineral density; DMD: Duchenne muscular dystrophy; LS: Lumbar spine; ZA: Zoledronic acid;