



Senior Medicine Rotation: Evidence-Based Medicine Project

Resident Name: Alex Reyentovich

Block:

Date: 11/28/04

Case SIGNOUT:

29 yo AA male inmate with known pulmonary sarcoid presented to CPMC from an outside hospital with ventricular tachycardia and a reduced EF of 15%. Initial attempts to pharmacologically control his rhythm as well as an attempt at ablation failed. Ventricular arrhythmias felt to be secondary to cardiac involvement of sarcoidosis and pt started on prednisone 1 mg/kg/day with near complete resolution of arrhythmia after 3 days. Pt advised to maintain on oral prednisone for at least 1 year. After reading the risks of the medications pt wants to do everything to avoid the complications of osteoporosis.

Clinical Question: Is there any evidence that bisphosphonates prevent osteoporosis in patient taking long term steroids?


Search Strategy

Database: Pubmed search

Placebo controlled and ("prevention and control"[Subheading] OR prevention[Text Word]) AND ("glucocorticoids"[MeSH Terms] OR "glucocorticoids"[Pharmacological Action] OR glucocorticoids[Text Word]) AND ("osteoporosis"[MeSH Terms] OR osteoporosis[Text Word]) AND (("diphosphonates"[TIAB] NOT Medline[SB]) OR "diphosphonates"[MeSH Terms] OR bisphosphonate[Text Word]) AND Randomized Controlled Trial[ptyp] AND English[Lang] AND "human"[MeSH Terms]


1: [Frediani B, Falsetti P, Baldi F, Acciai C, Filippou G, Marcolongo R.](#)

[Related Articles](#), [Links](#)

 Effects of 4-year treatment with once-weekly clodronate on prevention of corticosteroid-induced bone loss and fractures in patients with arthritis: evaluation with dual-energy X-ray absorptiometry and quantitative ultrasound.  
Bone. 2003 Oct;33(4):575-81.  
PMID: 14555261 [PubMed - indexed for MEDLINE]


2: [Brown JP, Olszynski WP, Hodsman A, Bensen WG, Tenenhouse A, Anastassiades TP, Ste-Marie LG, Kendler DL, Hanley DA, Josse R, Hanly JG, Lentle B, Jovaisas A, Ioannidis G, Stephenson GF, Barton I, Pack S, Chines A, Dias R, Adachi JD.](#)

[Related Articles](#), [Links](#)

 Positive effect of etidronate therapy is maintained after drug is terminated in patients using corticosteroids.  
J Clin Densitom. 2001 Winter;4(4):363-71.  
PMID: 11748341 [PubMed - indexed for MEDLINE]

3: [Reid DM, Adami S, Devogelaer JP, Chines AA.](#)

[Related Articles](#), [Links](#)

 Risedronate increases bone density and reduces vertebral fracture risk within one year in men on corticosteroid therapy.  
Calcif Tissue Int. 2001 Oct;69(4):242-7.

PMID: 11730260 [PubMed - indexed for MEDLINE]

- 4: [Adachi JD, Saag KG, Delmas PD, Liberman UA, Emkey RD, Seeman E, Lane NE, Kaufman JM, Poubelle PE, Hawkins F, Correa-Rotter R, Menkes CJ, Rodriguez-Portales JA, Schnitzer TJ, Block JA, Wing J, McIlwain HH, Westhovens R, Brown J, Melo-Gomes JA, Gruber BL, Yanover MJ, Leite MO, Siminoski KG, Nevitt MC, Sharp JT, Malice MP, Dumortier T, Czachur M, Carofano W, Daifotis A.](#) [Related Articles](#), [Links](#)
-  Two-year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids: a randomized, double-blind, placebo-controlled extension trial. *Arthritis Rheum.* 2001 Jan;44(1):202-11. PMID: 11212161 [PubMed - indexed for MEDLINE]
- 5: [Eastell R, Devogelaer JP, Peel NF, Chines AA, Bax DE, Sacco-Gibson N, Nagant de Deuchaisnes C, Russell RG.](#) [Related Articles](#), [Links](#)
-  Prevention of bone loss with risedronate in glucocorticoid-treated rheumatoid arthritis patients. *Osteoporos Int.* 2000;11(4):331-7. PMID: 10928223 [PubMed - indexed for MEDLINE]
- 6: [Cortet B, Hachulla E, Barton I, Bonvoisin B, Roux C.](#) [Related Articles](#), [Links](#)
-  Evaluation of the efficacy of etidronate therapy in preventing glucocorticoid-induced bone loss in patients with inflammatory rheumatic diseases. A randomized study. *Rev Rhum Engl Ed.* 1999 Apr;66(4):214-9. PMID: 10339777 [PubMed - indexed for MEDLINE]
- 7: [Geusens P, Dequeker J, Vanhoof J, Stalmans R, Boonen S, Joly J, Nijs J, Raus J.](#) [Related Articles](#), [Links](#)
-  Cyclical etidronate increases bone density in the spine and hip of postmenopausal women receiving long term corticosteroid treatment. A double blind, randomised placebo controlled study. *Ann Rheum Dis.* 1998 Dec;57(12):724-7. PMID: 10070271 [PubMed - indexed for MEDLINE]
- 8: [Pitt P, Li F, Todd P, Webber D, Pack S, Moniz C.](#) [Related Articles](#), [Links](#)
-  A double blind placebo controlled study to determine the effects of intermittent cyclical etidronate on bone mineral density in patients on long-term oral corticosteroid treatment. *Thorax.* 1998 May;53(5):351-6. PMID: 9708225 [PubMed - indexed for MEDLINE]
- 9: [Saag KG, Emkey R, Schnitzer TJ, Brown JP, Hawkins F, Goemaere S, Thamsborg G, Liberman UA, Delmas PD, Malice MP, Czachur M, Daifotis AG.](#) [Related Articles](#), [Links](#)
-  Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. Glucocorticoid-Induced Osteoporosis Intervention Study Group. *N Engl J Med.* 1998 Jul 30;339(5):292-9. PMID: 9682041 [PubMed - indexed for MEDLINE]
- 10: [Adachi JD, Bensen WG, Brown J, Hanley D, Hodsman A, Josse R, Kendler DL, Lentle B, Olszynski W, Ste-Marie LG, Tenenhouse A, Chines AA.](#) [Related Articles](#), [Links](#)
-  Intermittent etidronate therapy to prevent corticosteroid-induced osteoporosis. *N Engl J Med.* 1997 Aug 7;337(6):382-7. PMID: 9241127 [PubMed - indexed for MEDLINE]
- 11: [Reid IR, King AR, Alexander CJ, Ibbertson HK.](#) [Related Articles](#), [Links](#)
-  Prevention of steroid-induced osteoporosis with (3-amino-1-hydroxypropylidene)-1,1-bisphosphonate (APD). *Lancet.* 1988 Jan 23;1(8578):143-6. PMID: 2892989 [PubMed - indexed for MEDLINE]





**Senior Medicine Rotation: Based Medicine Project (Cont)**

Saag KG, Emkey R, et al. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. Glucocorticoid-Induced Osteoporosis Intervention Study Group. N Engl J Med. 1998 Jul 30;339(5):292-9

Group	Criteria or definition	n
Population screened.	15 center in the US and 22 centers in 15 other countries	Not clear
Inclusion criteria	Male and female 17-83 with underlying dermatologic, GI, pulmonary requiring >1 yr of at least 7.5 mg prednisone or equivalent	560
Exclusion criteria	Metabolic bone disease, low serum 25 vit D, currently taking calcitonin or bisphosphonate, pregnancy, creatinine clear <35, severe cardiac or upper GI disease	D
Treatment group	2.5, 5 or 10 mg of alendronate qd	83, 161 and 157
No treatment group	Placebo	159

Primary endpoints: Difference in the % change in lumbar spine bone density from baseline to 48 wks.

Secondary endpoints: Changes in bone density of the hip, biochemical markers of bone turnover and new vertebral markers.

- Are the Results of the Trial Valid?
  - Randomized? Yes
  - All patients accounted for at end? No. For primary endpoint 12 pts missing in the 10 mg group, 15 pts in the 5 mg group and 17 pts in the placebo group
  - Intention to treat? Yes-Data used from last BMD measurement if pt not available for 48 wk
  - Blinding? Yes
  - Groups similar at start of trial? Yes
  - Equal treatment of groups? Yes
  - Did randomization work? Yes
- Are the Results of the Trial important?
  - Size of treatment effect? -0.4 % in placebo, 2.1% in 5 mg, 2.9% in 10 mg
  - Precision of the estimate of the effect? Study only provides SE of the mean. If we calculate the SD based on our knowledge of the # of pts in the study group SD would be ~3.6 % in the treatment groups. Not a very precise measurement of effect.

Endpoint	Result	Significance	ARR	NNT
Bone mineral density	+2.1 and +2.9 % inc	<0.001		
Vertebral fractures	RR 0.6 (0.1-4.4)	0.18	-1.3	77
Morbidity	Result	Significance	ARI	NNH

- Can I apply these results to my patient?
  - Comparison of my patient to trial patients. My patient would potentially be excluded from this trial due to underlying “severe cardiac disease” though this is not defined. Otherwise our patient would be included.

- All clinically important outcomes considered. Bone density in the past has been shown to be a good surrogate for risk of fractures. Would like to have seen clinically (as opposed to radiographically) noted fractures sited. Study too brief and too small to show a difference in even radiographically noted fractures.
- Likely benefits outweigh potential harms and cost? Would like to see longer follow up to this study particularly seeing what happens to patients who stop steroids & bisphosphonates at 1 year. Are they protected against fractures in the long run? Other studies have shown a precipitous drop in bone mineral density once bisphosphonates are d/c'd. I think I would like to see longer follow particularly since our patient is so young. Nevertheless a well validated surrogate marker (change in bone density) clearly is improved in this study and the potential harms of this therapy are few. Of note though in this study with the placebo group taking >1000 mg of calcium + vit D there is very little bone density (-0.4%) over the course of 1 yr.