COLUMBIA UNIVERSITY MEDICAL CENTER

DIVISION OF GENERAL MEDICINE

Senior Medicine Rotation: Evidence-Based Medicine Project

Student Name: Katherine Goettsche **Block: August** **Date: 8/26/2010**

Case SIGNOUT:

61 yo man with h/o HTN, ESRD 2/2 FSGS s/p DDRT 2000 p/w worsening leg and sacral edema as in setting of DVT diagnosed 6 months ago - found to have proteinuria on UA & hypoalbuminemia with relatively preserved creatinine all concerning for nephrotic syndrome. 24-hr urine collection yielded 2.6 gm proteinuria indicating renal biopsy for diagnosis. Membranous glomerulonephritis was diagnosed in the donor kidney. Recommended treatment was 8 weeks of 120 mg prednisone qod, then taper by dropping by 20 mg every other day every 2 weeks (i.e. 120 every other day for 8 weeks, then 100 every other day for 2 weeks, then 80 every other day for 2 weeks, then 60 every other day for 2 weeks, then 40 every other day for 2 weeks, etc....) for a total of at least 4.5 months.

Clinical Question: Given that studies have shown 10 mg prednisone daily over a 4 month period reduces lumbar spine bone density, and that this patient is at risk for osteoporosis (after receiving steroids x 4.5 months at a much higher dose) which has implications for quality of life, is there a better treatment than bisphosphonates for glucocorticoid-induced osteoporosis?

Search Strategy
Database: Pubmed

Limits
- RCT
- 10 years
- Humans, English
- “prednisone-induced osteoporosis”

1. Effects of teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: thirty-six-month results of a randomized, double-blind, controlled trial.

Saag KG, Zanchetta JR, Devogelaer JP, Adler RA, Eastell R, See K, Krege JH, Krohn K, Warner MR.

Arthritis Rheum. 2009 Nov;60(11):3346-55.PMID: 19877063 [PubMed - indexed for MEDLINE]Related citations

☑ **2. Teriparatide or alendronate in glucocorticoid-induced osteoporosis.**

Saag KG, Shane E, Boonen S, Marín F, Donley DW, Taylor KA, Dalsky GP, Marcus R.

N Engl J Med. 2007 Nov 15;357(20):2028-39.PMID: 18003959 [PubMed - indexed for MEDLINE]Related citations

3. Alendronate or alfacalcidol in glucocorticoid-induced osteoporosis.

de Nijs RN, Jacobs JW, Lems WF, Laan RF, Algra A, Huisman AM, Buskens E, de Laet CE, Oostveen AC, Geusens PP, Bruyn GA, Dijkmans BA, Bijlsma JW; STOP Investigators.

N Engl J Med. 2006 Aug 17;355(7):675-84.PMID: 16914703 [PubMed - indexed for MEDLINE]Related citations

4. Changes in bone mineral density following discontinuation or continuation of alendronate therapy in glucocorticoid-treated patients: a retrospective, observational study.

Emkey R, Delmas PD, Goemaere S, Liberman UA, Poubelle PE, Daifotis AG, Verbruggen N, Lombardi A, Czachur M.

Arthritis Rheum. 2003 Apr;48(4):1102-8.PMID: 12687554 [PubMed - indexed for MEDLINE]Free ArticleRelated citations

5. Summaries for patients. Prednisone for rheumatoid arthritis.

[No authors listed]

Ann Intern Med. 2002 Jan 1;136(1):I-26. No abstract available. PMID: 11777372 [PubMed - indexed for MEDLINE]Free ArticleRelated citations

6. Low-dose prednisone therapy for patients with early active rheumatoid arthritis: clinical efficacy, disease-modifying properties, and side effects: a randomized, double-blind, placebo-controlled clinical trial.

van Everdingen AA, Jacobs JW, Siewertsz Van Reesema DR, Bijlsma JW.

Ann Intern Med. 2002 Jan 1;136(1):1-12.PMID: 11777359 [PubMed - indexed for MEDLINE]Free ArticleRelated citations

7. Two-year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids: a randomized, double-blind, placebo-controlled extension trial.

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.

Arthritis Rheum. 2001 Jan;44(1):202-11.PMID: 11212161 [PubMed - indexed for MEDLINE]Free ArticleRelated citations

Senior Medicine Rotation: Based Medicine Project (Cont)

Group	Criteria or definition	n
Population screened.	men and women in North and South America, women in Europe	712
Inclusion criteria	- age ≥21 - history of sustained glucocorticoid therapy (mean daily dose of 5 mg or more prednisone for 3 or more months immediately preceding screening visit – considered a reasonable threshold for long-term use based on basis of international guidelines) - T score (lumbar spine or hip) either - i) -2.0 or less, or -ii) -1.0 or less in addition to one fragility fracture (trauma equivalent to fall from standing height or less) during treatment with glucocorticoids	429
Exclusion criteria	- ≤3 lumbar vertebrae able to evaluate on DEXA - substantial renal impairment by Cockcroft-Gault formula - abnormal thyroid function - bisphosphonate treatment for >2 weeks within 6 months before enrollment or for > 2 years within the previous 3 years - nontrivial exposure to other osteoporosis therapies	219
Treatment group	Randomized to: - injectable (sc) teriparatide 20 µg plus oral placebo or - alendronate 10 mg po plus injectable (sc) placebo Both groups received calcium carbonate (1000mg elemental Ca) and vitamin D (800 IU) daily Follow-up evaluations at 1, 3, 6, 12 and 18 months Compliance assessed by interviewing patients and quantifying oral and injectable medications returned to investigators.	428 214 – teriparatide (150 completed) 214 – alendronate (144 completed)
No treatment group		

Primary endpoints:

- Change from baseline to 18 months in bone mineral density at lumbar spine associated with daily either i) teriparatide 20 mcg or ii) alendronate 10 mg in patients with already-established glucocorticoid-induced osteoporosis

Secondary endpoints:

- changes in bone mineral density at total hip: scans withheld from investigators unless patient reached pre-specified safety value of loss of >8% of bone. Lumbar vertebrae fractured during the trial were excluded from calculation of bone mineral density.
- markers of bone turnover: bone formation markers (N- and C-terminal pro-peptides of type I collagen, bone-specific alkaline phosphatase) and bone resorption maker (C-telopeptide of type I collagen) were measured in serum from a subgroup of 199 patients after overnight fasts at 1,6 and 18 months for analysis.

- time to changes in bone mineral density at lumbar spine and total hip
- incidence of vertebral and nonvertebral fractures
- adverse events (hypercalcemia, hyperuricemia, injection site reactions, headache, dizziness)

- Are the Results of the Trial Valid?
    - Randomized? Yes
    - All patients accounted for at end? Yes
    - Intention to treat? Yes
    - Blinding? Yes
    - Groups similar at start of trial? Yes

	Age (yrs)	Male (%)	% of women who are postmenopausal	Prednisone daily dose x duration (mg x yr)	Lumbar Spine T Score
Teriparatide	56.1 ± 13.4	19.6%	77.9%	11.25	-2.5 ± 0.88
Alendronate	57.3 ± 14	19.2%	82.7%	9.36	-1.9 ± 0.91

    - Equal treatment of groups? Yes
    - Did randomization work? Yes
- Are the Results of the Trial important? Yes: adherence to treatment in Teriparatide and Alendronate groups respectively for injection: 98.7% and 97.6% and for oral: 94.3% and 93.2%. Statistically significant results showed clinical benefit.
    - Size of treatment effect? Yes
    - Precision of the estimate of the effect? Yes

Endpoint	**Result**	**Significance**	**ARR**	**NNT**
Increase from baseline bone density at Lumbar Spine	7.2±0.7% Teriparatide 3.4±0.7% Alendronate	p<.0001		
Increase from baseline bone density at Total Hip	3.8±0.6% Teriparatide 2.4±0.6% Alendronate	p<.005		
Morbidity	**Result**	**Significance**	**ARI**	**NNH**
Adverse event possibly related to treatment	Teriparatide 17.8 Alendronate 13.1	p .019		
Nonvertebral fracture	Teriparatide 5.6 Alendronate 3.7	p .36		

- Can I apply these results to my patient?
    - Comparison of my patient to trial patients.
        - My patient is being prescribed a course of prednisone that qualifies him for eligibility in this study. We do not have a baseline T score for him as he just started this treatment; he will receive at least 5700 mg over at least 4.5 months and based on this it is reasonable to conclude that he will be vulnerable to secondary osteoporosis. This is consistent with study participants, who received initial screening for osteoporosis after completing prednisone course.
        - Perhaps more importantly, given the indication for prednisone as treatment for membranous glomerulopathy, it is worthwhile to note that his renal function does not preclude treatment with bisphosphonates. Using the Cockcroft-Gault equation, his creatine clearance was 53-65 cc/min. Alendronate is contraindicated for creatine clearance <35 cc/min. Teriparatide has not been tested extensively in post renal transplant patients.
        - Age very close to average for study, although study population includes primarily post-menopausal women

- Indication for prednisone: approximately 10% of study population, like my patient, fall under "other" category. One future direction might look at teriparatide vs alendronate in populations of patients with steroid-induced osteoporosis for similar underlying medical problems ie cohort of patients on prednisone specifically for RA)

- All clinically important outcomes considered.
  - Primary and secondary endpoints consider clinically relevant consequences of osteoporosis,
  - Also considers adverse effects including side effects of medications
  - Study accounts for diverse medical conditions indicating treatment with steroids and documents these

- Likely benefits outweigh potential harms and cost? Yes, on a case-by-case basis. In this case, given that this patient is s/p renal transplant now with membranous glomerulonephritis, I would be hesitant to initiate either agent empirically after prednisone course completed, given potential for renal toxicity, unless symptoms of osteoporosis presented in which case benefits might outweigh risks.
  - Benefits
    - Improved bone density at lumbar spine (primary outcome) with teriparatide
    - Teriparatide was more successful than Alendronate in most secondary outcomes (total hip densiry, fewer vertebral fractures * underpowered for this); no significant difference between groups for non-vertebral fractures and adverse events
  - Risks
    - Study does not assess baseline bone density prior to starting steroids
    - Cumulative exposure is not addressed, ie steroids received during study period
    - Primary outcome is bone density, but what is the clinical relevance of this to the patient? (ie symptomatic osteoporosis might be a better primary outcome if considering quality of life in a patient with complex medical problems)
    - Teriparatide is expensive: for one month Alendronate $100, Teriparatide $900
    - Teriparatide safety in chronic kidney disease/renal transplant patients not yet well studied