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◆ EDITORIAL

This Medifile issue reviews 3 topical subjects following recent publications. Firstly, the safety concerns on the long acting β 2-adrenergic agonists (LABAs) are discussed, following the recent safety warnings published by the FDA. Next, the outcomes of the Fosamax Actonel Comparison Trial (FACT), published in 2005, are reviewed with a focus on the practical application of the trial results in terms of reduction of fracture risk. Finally, we provide an overview of existing and current studies on the relationship between male circumcision and the possible reduction of HIV infection, following the publication of the results of the South African Male circumcision in HIV randomized controlled trial (the ANRS 1265 Trial).

2. COMPARISON OF ALENDRONATE- AND RISEDRONATE-ONCE-WEEKLY THERAPY IN POSTMENOPAUSAL OSTEOPOROSIS

BACKGROUND

Women with postmenopausal osteoporosis are more susceptible to low trauma fractures.¹ This is due to an increased rate of bone turnover, where bone resorption exceeds bone formation.² Bone resorption is mediated by osteoclasts (multinucleated cells that consume bone tissue during the resorption process of the bone remodeling cycle).³ In menopausal women, osteoclast activity is increased because of decreased oestrogen levels.⁴ The resultant decline in bone volume, bone density and bone strength predisposes to fractures,¹ with vertebral and hip fractures being associated with pronounced morbidity and increased mortality.⁵ Thus, there is a genuine need to regulate, especially inhibit, bone resorption rate in osteoporosis.

The National Osteoporosis Foundation (NOF) has published a guideline, *Five Steps to Bone Health and Osteoporosis Prevention*. On NOF's recommendation, these steps are most effective when used in combination, as no one step alone may be adequate to prevent osteoporosis.

The five steps are:

1. Consume recommended amounts of calcium and vitamin D daily
2. Engage in regular weight-bearing exercise
3. Avoid smoking and excessive alcohol
4. Discuss bone health with a healthcare provider
5. Have a bone density test and take medication *when appropriate*⁶

The mainstay of osteoporosis treatment is bisphosphonate therapy. Bisphosphonates are anti-resorptive pharmacological agents that decrease fracture risk by reducing the rate of bone remodelling.² Several modes of action of the bisphosphonates have been postulated including inhibition of osteoclast activity (directly or indirectly) and induction of apoptosis (premature cell death) of osteoclasts.⁷ In South Africa bisphosphonates approved for the treatment of osteoporosis that are available as a once-weekly (OW) dose include alendronate (Fosamax[®] 70mg) and risedronate (Actonel[®] 35mg).

THE FACT STUDY

Study design

A 12-month randomised, double-blind, multicenter comparative study, the **Fosamax Actonel Comparison Trial** (FACT study), was conducted to compare the efficacy and tolerability of these two OW pharmacological agents. The results were published in the January 2005 issue of the *Journal of Bone and Bone Mineral Research*. The study was designed as a 12-month bone mass densitometry (BMD) trial with an additional 12-month extension, during which patients were maintained on blinded

study medication. Outcome measurements were only indicated at 6 and 12-month intervals.²

1,053 postmenopausal women with low BMD, defined by a BMD of $>$ or $=$ 2.0 standard deviations below young normal mean bone mass, were randomised to either alendronate (N=520) or risedronate (N=533) OW. In addition to study medication, all patients were to take 1000mg of elemental Calcium and 400IU of vitamin D daily, for the duration of the study period.

The endpoints analysed included changes in *bone mass densitometry* (BMD) and biochemical *bone resorption markers* (BCMs).² BCMs are used to identify patients with high bone turnover. These biochemical tests provide different but complementary information to BMD measurement that can aid in predicting risk of future bone loss and osteoporotic fracture.^{2,8}

Gastrointestinal tolerability was evaluated in a subgroup analysis by adverse experience (AE) reporting.²

Assessment of outcomes

Study results at the end of 12 months showed that alendronate increased BMD 62% more than risedronate (3.4% vs. 2.1%; $p < 0.001$) at the hip trochanter, which was the primary endpoint of the study. At other sites, alendronate showed similar gains: 83% more for the total hip (2.2% vs. 1.2%; $p < 0.001$); 78% more at the femoral neck (1.6% vs. 0.9%; $p = 0.005$) and 42% more at the lumbar spine (3.7% vs. 2.6%; $p < 0.001$). Differences were significant as early as six months on bisphosphonate therapy and were maintained at 12 months.²

Fewer alendronate than risedronate patients experienced bone loss at the hip trochanter (4.7% vs. 11.0%; $p < 0.001$) and at the lumbar spine (1.3% vs. 4.1%; $p = 0.008$).²

Other secondary endpoints, such as BCM's were also investigated. Alendronate showed a significant greater reduction in bone turnover than risedronate:²

- *Bone resorption markers*: in the alendronate group urinary N-telopeptide (NTx) decreased by 12.6% more (95% CI: -16.6, -8.5; $p < 0.001$) and serum C-telopeptide (CTX) of type-I collagen decreased by 19.1% more than the risedronate group.
- *Bone formation markers*: bone-specific alkaline phosphatase (BSALP) and serum procollagen type 1-N-terminal peptide (P1NP) showed a treatment difference of -12.5% ($p < 0.001$) and -15.9% ($p < 0.001$) respectively, in favour of the alendronate group.

Significant differences in all BCMS were seen as early as 3 months and were maintained throughout the 12-month study.²

The comparative tolerability of the two drugs was similar between both treatment groups, with upper gastrointestinal (GI) adverse events (AEs) occurring in 20.1% of the risedronate study group vs. 22.5% in the alendronate study group ($p = 0.364$). The most common upper GI AE reported was dyspepsia (8.2% in the alendronate-treated patients and 7.8% in the risedronate-treated patients) and gastro-oesophageal reflux disease (GORD) was reported in 2.7% versus 3.0% in the alendronate and risedronate groups, respectively (See Table 2.1).²

Implications

The relevant question is: "What are the main clinical implications of the FACT study results?" This head-to-head study of alendronate and risedronate in similar population groups given the same dosing instructions, showed a significant difference in BMD (at all sites) and BMCs. Thus, alendronate seems to reduce the rate of bone remodelling to a greater extent than risedronate.



Table 2.1 Incidence of Adverse Experiences²

Adverse experiences	Alendronate 70mg once weekly (n=515)		Risedronate 35mg once weekly (n=527)	
	n	%	n	%
Any	394	76.5	399	76.1
Serious	45	8.7	41	7.8
Causing discontinuation	33	6.4	33	6.3
Upper gastrointestinal				
Any	116	22.5	106	20.1
Causing discontinuation	13	2.5	16	3.0

(Source: Rosen Clifford (et al), Treatment with Once-Weekly Alendronate 70mg compared with Once-Weekly Risedronate 35mg in Women with Postmenopausal Osteoporosis: A Randomized Double-Blind Study. JBMR, January 2005; 20(1):141)

Even though the FACT study measured BMD and BCMs as the surrogate endpoint markers,² some opinion leaders mention that the *real end point that should be considered is the reduction of fractures*.^{9,10} This is due to the fact that the relationship between BMD and BMC changes and reduction of fracture risk with antiresorptive therapy of osteoporosis is not fully understood.^{2,10,11} The increase in BMD following treatment depends on the baseline bone remodelling rate (which differs from patient to patient), the dose of the drug administered, and the drug's potency.¹⁰

The reduced fracture incidence may be due to structural changes that are not indicated in the BMD scan.¹⁰ Delmas et al cautioned that the increase in BMD was not consistent with the fracture risk reduction in all meta-analyses.¹¹ Dr Rosen, the main author of FACT, suggested that if fracture rates were to be evaluated, it would require a sample size of > 50,000 patients to adequately evaluate a difference between alendronate and risedronate. The resultant cost and logistics would be problematic.²

CONCLUSION

The FACT study concluded that "greater gains in BMD and greater reductions in markers of bone turnover were seen with alendronate compared with risedronate with similar tolerability."² However, the difference in BMD and BMCs between these two pharmacological agents does not provide absolute evidence that the one drug is more efficacious than the other in reducing fracture risk. Further studies are needed to compare the fracture-rate reduction.

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