Rapid Trabecular Bone Loss After Cardiac Transplantation Using FK506 (Tacrolimus)-Based Immunosuppression


The macrolide lactone tacrolimus (FK506) is a new immunosuppressive drug that has demonstrated to be 10 to 100 times more potent than cyclosporine A. After forming a complex with the immunophilin FK506-binding protein, the complex acts in a similar fashion to the cyclosporine-immunophilin complex, resulting in an inhibition of calcineurin, a calcium-dependent serine/threonine protein phosphatase. This inhibition prevents the assembly of the functional transcription of interleukin 2. Although tacrolimus has reputedly less severe side effects, recent experimental studies have demonstrated an increase of bone formation and bone resorption, accompanied by a significant reduction in percent trabecular area. The present study was undertaken to assess the effects of tacrolimus-based immunosuppression on bone mineral metabolism after orthotopic heart transplantation.

METHODS

Seven patients (six male, one female; mean age: 51 ± 10 yrs) were studied before and 3 ± 2 months after heart transplantation (HTx) to evaluate the immediate effects of tacrolimus-based immunosuppression on bone density, fracture rate, and disturbances in biochemical markers. Time interval between both examinations was 9 ± 2 months. Aside from FK506 (mean blood level 13 to 18 ng/mL, radioimmunoassay), immunosuppressive regimen included azathioprine and steroids.

Bone mineral density (BMD, g/cm²) was measured at the lumbar spine (L2-L4) using dual-energy x-ray absorptiometry (DEXA, Lunar Expert-XL, Madison, Wisc). Vertebral bone density (VBD) was evaluated by single energy computer tomography after HTx. Results were expressed as VBD values ±SD, BMD T-values ± SD, and as percentage of variation from baseline. Vertebral fractures were assessed by x-rays of chest, thoracic, and lumbar spine.

Biochemical markers included gonadal hormones, gonadotropins, urinary and serum parameters of calcium metabolism, intact PTH, 25OHD, and renal function. Data were compared between consecutive measurements as well as to age-matched controls.

RESULTS

All patients showed significantly impaired bone mineral density before transplantation (~1.3 ± 0.7 g/cm²; 87 ± 7%) compared to normals. After HTx a further decline in BMD (~1.6 ± 0.7 g/cm²; 84 ± 7%) was seen within an average of 3.1 ± 1.6 months. VBD was also significantly decreased after HTx (75 ± 29 mg/ccm versus 125 ± 25 mg/ccm, P < .01). No fracture was documented. There were no significant differences in biochemical parameters of calcium metabolism, intact PTH, gonadotropins, and renal function before and shortly after HTx. Testosterone levels decreased in five of six male patients, with an average of 1.7 ng/mL (range 0.08 to 5.22 ng/mL). One patient became hypogonadal after HTx. Luteinizing hormone increased significantly within the normal range from 3.4 ± 0.9 mU/mL to 6.2 ± 1.5 mU/mL (P < .001). Follicle stimulating hormone remained unchanged within the normal range.

CONCLUSION

Despite preexisting reduced bone density, these preliminary data demonstrated a rapid further reduction on bone mineral density due to a tacrolimus-based immunosuppressive regimen that may lead to future fractures. The precise mechanisms on bone mineral metabolism of each individual immunosuppressive agent are difficult to examine because of the combination therapy in clinical settings. Besides the well-known negative effects of steroids on bone mineral metabolism, tacrolimus may have a direct toxic effect on bone cells and the secretion of local autocrine factors. Second, the agent may have indirect effects on bone via a modulation of cytokines and gonadal dysfunction.

The role of tacrolimus on steroidogenesis of Leydig cells is still controversial. Eighty percent of our study population showed a decrease of testosterone levels, which may contribute to trabecular bone loss. There was only a slight increase in lutenizing hormone levels, which might be due to only one hypogonadal patient. These results are in contrast to experimental data by Tai et al who found no direct inhibitory effect of tacrolimus on testosterone biosynthesis in rat Leydig cells. Cyclosporine A, with its similar
biologic action, also impairs testicular steroidogenesis and spermatogenesis in rats\(^3\) and humans\(^4\) mediated through the hypothalamic-pituitary axis and direct inhibition of testosterone biosynthesis enzymes.

In summary, these preliminary data in patients with tacrolimus-based immunosuppression indicate the necessity to monitor carefully bone mineral metabolism and to administer a therapy to prevent further bone loss.

REFERENCES