Editorial

Balancing Bones and Bucks Among New Glucocorticoid Users

The major limitation of therapy with synthetic glucocorticoids remains the predictable decline in bone mass and the increased fracture risk that afflicts many patients receiving longterm therapy. Recent data suggest a deleterious effect of even very low dose short term therapy on bone health, raising concern that strategies to prevent bone loss should be considered sooner rather than later[1]. Despite a slowly increasing array of prescription anti-osteoporotic therapies efficacious for increasing bone mass among glucocorticoid users[2-5], the majority of such patients receive neither bone mass measurement nor even simple interventions such as calcium and vitamin D[6,7]. Routine bone mineral density (BMD) testing and a more aggressive therapeutic approach for glucocorticoid users have been recommended by a variety of specialty organizations and consensus groups[8-11]. Variations in physicians' knowledge and attitudes[12], concerns about the cost and inconvenience of polypharmacy, and difficulty making time to address osteoporosis issues in patients with numerous serious medical problems are among the many suspected barriers to adoption of recommendations[13]. However, even among those health care providers who frequently address bone health issues among their glucocorticoid users, it is often difficult to decide which patients merit a more aggressive treatment plan (typically, the addition of a bisphosphonate medication), and which patients are at a low enough risk to justify a more conservative approach with sufficient calcium, vitamin D, and careful surveillance.

Under optimal circumstances, concerned clinicians rightfully recommend the most effective treatment modality for each medical condition afflicting their patients. Despite this intent, in an era of international escalation in health care costs, not all patients routinely receive every therapy of potential benefit. Indeed, when several effective and reasonably safe therapies co-exist for a preventable outcome, a cheaper option, even if marginally less effective, may be chosen over one that is more costly. Formal cost-effectiveness analyses using decision analytic techniques apply variable levels of methodological rigor to questions of this nature in hopes of providing guidance to policy makers and potentially to clinicians.

The article by Buckley and Hilner in this issue of *The Journal*[14] is one of just a few recent cost-outcome studies assessing glucocorticoid-induced osteoporosis (GIOP). Previously, Solomon and Kuntz used a Markov decision model to examine the incremental cost-effectiveness (C/E) of different bone loss management strategies for patients initiating glucocorticoids[15]. Hypothetical treatment approaches ranged from "watchful waiting" (treatment only after a fracture occurs — an option that few clinicians would consider acceptable in 2002) to empirical treatment with either alendronate or etidronate. Compared to watchful waiting and treatment with alendronate, the cost per quality adjusted life year (QALY) was $92,600 (in year 2000 US dollars) for treatment with alendronate for patients with a T score of –1.0 (a BMD threshold recommended by an American College of Rheumatology consensus panel[16]). Cost dropped to $76,100 per QALY if the BMD threshold was lowered to a T score ≤ 2.5. The authors concluded that both these costs per QALY were higher than many well-accepted medical interventions[17,18]. In their carefully conducted analysis, the base case assumed only a 12.5% reduction in fracture rate with alendronate. On the other hand, if a 25% reduction in fracture risk had been assumed, the incremental cost-effectiveness for treating with alendronate decreased slightly to $50,000 per QALY. If therapy resulted in a 50% reduction in fracture risk, the cost would have dropped to below $19,000 per QALY. It should be noted that although bisphosphonate data for nonvertebral fractures among glucocorticoid users are not available, a 25% and perhaps even a 50% risk reduction in nonvertebral fractures is not beyond reason, based on extrapolation of data from bisphosphonate studies in postmenopausal women.

Buckley and Hilner provide us with another thoughtful and provocative cost-effectiveness study of therapeutic approaches to patients initiating glucocorticoids[14]. The hypothetical patients providing outcome and cost estimates in this study are women without osteoporosis who are beginning glucocorticoids at different ages. Outcomes are reported as cost per vertebral fracture avoided rather than QALY. The authors justify

See A cost effectiveness analysis of calcium and vitamin D supplementation, etidronate, and alendronate in the prevention of vertebral fractures in glucocorticoid treated women, *page 132*

not using QALY based on the absence of rigorously determined patient-based preferences (i.e., utility weights) for these particular fracture health states. The base-case model in this analysis contains reasonable assumptions and the use of sensitivity analyses to examine the impact of marked variations in assumptions further strengthens a generally solid analysis. Risedronate is notably absent from both this and the Solomon and Kuntz analysis[15]. Nonetheless, risedronate has very similar costs and efficacy data compared to alendronate for glucocorticoids users. Thus, had risedronate been considered instead of alendronate it would not likely have changed the key findings appreciably. The study is further strengthened by the inclusion of indirect costs in the analysis, thereby accounting for some of the often neglected costs of lost productivity that result from fractures.

Both this study and the one by Solomon and Kuntz, which accounted for both vertebral and non-vertebral fractures, report cost-effectiveness advantages for less aggressive approaches to prevention among lower risk patients. Although etidronate had superior marginal cost-effectiveness to alendronate in the Buckley and Hilner report, the absence of a convenient weekly etidronate preparation and the availability of 2 current and other more potent bisphosphonates in development make it unlikely that etidronate will assume a more central role in GIOP prevention, despite these findings.

One limitation of this study is the assumption that fracture risk and fracture prevention are mediated exclusively by changes in BMD. High dose glucocorticoids can lead to osteoblast and osteocyte apoptosis[19] such that fractures may occasionally occur even after short time intervals and with relatively well preserved BMD. Further, the fracture risk model is derived from clinical trials using patients who are not taking corticosteroids, potentially leading to a conservative estimate of fracture risk in the older patient. If the rate of fracture was doubled in all age groups, etidronate and alendronate treatment were more cost-effective in the life-time analysis: < $10,000 and < $4000 per fracture avoided, respectively. Another limitation of this analysis is the hopeful assumption that improvement in BMD seen with calcium and vitamin D translates into fracture risk reduction. Calcium and vitamin D increase BMD among patients who are chronic glucocorticoid users[20] and in the control arms of the clinical trials may attenuate bone loss compared to what would be historically expected[3,4]. Further data, however, are still needed to test the tenable hypothesis that calcium/vitamin D alone can reduce fracture risk in GIOP. While a similar argument might be raised against the bisphosphonate data, there are at least secondary analyses and results from extension studies to support 70 to 90% vertebral fracture risk reduction[21,22].

So, how should the busy clinician who is concerned about the musculoskeletal side effect of glucocorticoids react to the findings from this decision analysis? As the authors themselves indicate, a primary purpose of this study and others of its type is not to specify treatment for an individual patient, but to challenge existing guidelines and highlight data gaps. As the clinical trial data would lead us to believe, there are certain low-risk patients for whom a less aggressive approach may be warranted, provided these patients are closely monitored. On the other hand, very few of the highest risk patients were included in these GIOP clinical trials. As was suggested by both decision analyses cited and is mandated by an unequivocally and unacceptably high fracture rate, high risk patients (i.e., those with multiple other fracture risk factors such as estrogen deficiency, elders at high fall risk, etc.) and those using high dose glucocorticoid therapy necessitate a uniformly aggressive treatment approach. Caring for patients with chronic inflammatory diseases remains a delicate balancing act between providing benefits and causing harms. For better or worse, drug cost has become an increasingly heavy weight on the risk-benefit scale and one that has the potential to tip the balance away from a benefit to bones.

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