Editorial

First Do No Harm — A Bone of Contention in Rheumatoid Arthritis

Jolles and Bogoch, in this issue of *The Journal*, discuss current consensus recommendations for treatment of rheumatoid arthritis (RA) and conclude that there are blind spots related to the prevention and treatment of osteoporosis in RA[1]. They present what would appear to be an open and shut case: a description of increased fracture risk in RA with and without steroids, a consensus statement suggesting that corticosteroids should be avoided due to unacceptable side effects, a statement that treatments are available that can prevent the osteoporosis and reduce the fracture risk, and a condemnation of guideline producers for their failure to address the issue. However, there are other, recently published consensus guidelines that do recommend treatment with corticosteroids in RA and that also recommend osteoporosis prevention[2]. Perhaps the blind spot is in the fact that clinicians are not aware of or do not respond to the published guidelines?

There remain many unanswered questions. What is the incidence of fracture in early RA? Does the fracture risk vary over time? Will we even be able to answer these questions now given that the pyramid has been inverted and international consensus recommends that RA be treated earlier and more aggressively to attain a state of low disease activity? What influence does RA therapy have on fracture risk? What role should corticosteroids play in the treatment of RA? Are they friend or foe when it comes to bone density and fracture risk? Could their earlier use gain initial control of disease activity and actually prevent bone loss? What role does early periarticular osteopenia play in the subsequent development of joint damage? Do guidelines address the issue sufficiently? Both the American and British rheumatology societies have published guidelines for the prevention of corticosteroid induced osteoporosis. But do clinicians actually follow the guidelines? Are our eyes wide shut?

Hippocrates would have us "make a habit of two things," suggesting that with relation to disease we should "help or at least to do no harm."

Ever since Hench first described the miraculous effect of compound E on a patient with RA[3], the rheumatological profession has had a love–hate relationship with corticosteroids. There is no arguing the dramatic antiinflammatory action of steroids in joint disease, but the apparent lack of prolonged effect, coupled with a side effect profile that today would strike fear in the heart of any regulatory body, has resulted in a general cautionary attitude toward their use. Nevertheless, corticosteroids have become an important part in the management of a wide range of chronic and often life-threatening respiratory, gastrointestinal, and connective tissue diseases.

There is surprisingly little conclusive evidence to direct us in the optimal use of corticosteroids in RA[4]. Short term use gives a marked symptomatic effect[5], but controversy exists as to the magnitude of benefit arising from longer duration of therapy and the most appropriate dosage for clinical effect while minimizing side effects[6]. There is growing evidence that corticosteroids impart limited disease modifying activity in addition to their well recognized antiinflammatory action; van Everdingen and colleagues[7] have this year shown a reduction in radiological joint damage with 10 mg/day of prednisone in early disease modifying antirheumatic drug-naive RA compared to placebo.

Current American College of Rheumatology (ACR) guidelines for the treatment of RA place low dose (< 10 mg/day prednisone equivalent) steroids as a part of symptom control, and as helpful to control disease activity, alleviate pain, and improve function. The caveat is that the clinician must consider adverse events with corticosteroids in the equation, in particular that of glucocorticoid induced osteoporosis. The article by Jolles and Bogoch[1] highlights the importance of recognizing the need for osteoporosis prevention and treatment in managing patients with RA.

It is well recognized that RA per se is associated with an increased risk of generalized osteoporosis and with bone mineral density (BMD) lost early in the disease, and is associated with disease activity[8,9]. There are no well designed sufficiently powered epidemiological studies that have addressed the

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true incidence of fracture in this population, and given the prevalence of corticosteroid use and early intervention now in RA, this is unlikely to be resolved. We are left to infer that the lower BMD brings with it a higher fracture risk. Michel, *et al*[10] looked at a large database of rheumatoid patients, and found that pre-existing osteoporosis in this population was an important risk factor for fracture, independent of steroid use.

Corticosteroid therapy is well known to be independently associated with bone loss, particularly in the first 6 months of therapy[11,12]. The dose of prednisone at which osteoporosis needs to be considered has been a subject of contention that is still not definitively settled; doses over 7.5 mg/day are accepted to incur significant bone loss and increased fracture risk[13], but doses below this are controversial[14,15]. Van Staa, *et al*[16] have shown an odds ratio (OR) of 1.61 for hip fracture in patients taking corticosteroid versus controls. When different doses were considered, low dose (< 2.5 mg/day) did not confer an increased OR, moderate dose (2.5–7.5 mg/day) increased the OR to 1.77, and higher doses to an OR of 2.27. In reality, our patients with RA are unlikely to be maintained on doses less than 2.5 mg/day, and so we must infer an increased risk of fracture due to corticosteroids in this population.

Recent studies of steroid induced bone loss in patients with RA have not defined the problem any better[17], some studies showing bone loss increased on low dose steroid and others suggesting improved disease control due to the steroid therapy may ameliorate bone loss. Sambrook, *et al*[18] have recently shown that low dose corticosteroid therapy in RA is associated with a further small decrease in bone mass in addition to the disease related bone loss, but this failed to reach statistical significance. A cross sectional study of 139 patients with RA[15] showed patients receiving prednisone doses of 1–4 mg/day had similar BMD to those not receiving any steroid, but higher doses were associated with significantly lower BMD at the lumbar spine. There was no significant effect seen at the femoral neck.

The ACR guidelines for the management of RA[2] address osteoporosis as an important consideration for the use of corticosteroids, and recommend calcium and vitamin D supplementation in all patients taking steroids. As bisphosphonates are effective in preventing bone loss, it is recommended they be considered at the time of initiating corticosteroid therapy. Despite the convincing science behind this argument, most governments and health systems will not subsidize the use of bisphosphonates without evidence of a low-trauma fracture, thus limiting the ability of clinicians and their patients to respond to the prevention of corticosteroid induced osteoporosis, even if they were aware of the guidelines. The lack of fracture endpoint data and the short term nature of many of the studies make it difficult to judge the true cost effectiveness of this recommendation.

Guidelines published for the specific management of glucocorticoid induced osteoporosis[19,20] are similar in message although they differ in the steroid dosage and BMD thresholds considered clinically important. This simply highlights the confusion that surrounds the effect of corticosteroids on bone.

Glucocorticoid induced osteoporosis is an important consideration for all clinicians, but particularly for the rheumatologist who not only has an interest in matters of bone, but also uses corticosteroids as a part of his or her pharmaceutical armamentarium on a daily basis. Guidelines on how to prevent and manage this condition, although not prescriptive, exist to help guide one in day-to-day practice.

It is concerning, therefore, to be reminded of how infrequently clinicians are recognizing, let alone managing, iatrogenic osteoporosis effectively. It is small consolation that rheumatologists are somewhat better at it than other clinicians[21,22].

A recent Canadian survey carried out by Soucy, *et al*[23] found that about 50% of rheumatologists follow ACR guidelines for prevention and treatment of corticosteroid induced osteoporosis. Use of BMD measurement was variable; Hougardy and colleagues[24] found that only 26% of patients taking longterm steroid therapy had had their BMD measured; Smith and colleagues[21] found only 47% had been offered BMD. T score cutoffs, corticosteroid dosage, and duration of corticosteroid therapy as a guide for osteoporosis treatment are also variable[23]. Surveys of hospital inpatients do not show improved adherence to accepted guidelines; Peat and colleagues[25] found only 5.6% of patients taking corticosteroids were receiving appropriate prophylaxis. In a survey of 92 patients taking steroids in a general medical ward[26], 64.7% were not receiving any treatment for osteoporosis, and 35.7% were receiving treatment not recommended in published guidelines. In another hospital cohort, Hougardy, *et al*[24] found 62% of longterm steroid users were not getting sufficient appropriate exercise and 35% had low oral calcium intake and 26% low sunlight exposure, reinforcing the need for more simple measures in the maintenance of bone health. A large population based observational study[27] has shown only 0.5% of patients taking low dose steroids received bisphosphonates, and 0.1% vitamin D supplements.

There is an obvious disconnection between available guidelines and their implementation that needs to be addressed. What if our cardiology colleagues were to find similar compliance rates for thrombotic prophylaxis in their patients with coronary artery disease? There is no good excuse for ignoring the important issue of glucocorticoid induced osteoporosis while there are readily available treatment guidelines and intervention strategies. We need to look at methods of increasing awareness, among both physicians and the general community, of this important public health issue and the available treatment options.

Robert Ingersoll claimed that "It is an old habit with theologians to beat the living with the bones of the dead." Perhaps we should all be looking a little closer at the bones themselves.

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REFERENCES

1. Jolles BM, Bogoch ER. Current consensus recommendations for rheumatoid arthritis therapy: a blind spot for osteoporosis prevention and treatment. J Rheumatol 2002;29:xxxx.
2. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 update. Arthritis Rheum 2002;46:328-46.
3. Hench PS, Kendall EC, Slocumb CH, Polley HF. The effect of a hormone of the adrenal cortex (17-hydroxy-11-deyhydrocorticosterone: Compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis. Proc Staff Meet Mayo Clin 1949;24:181-97.
4. Saag KG, Criswell LA, Sems KM, Nettleman MD, Kolluri S. Low-dose corticosteroids in rheumatoid arthritis. A meta-analysis of their moderate-term effectiveness. Arthritis Rheum 1996;39:1818-25.
5. Gotzsche PC, Johansen HK. Meta-analysis of short-term low dose prednisolone versus placebo and non-steroidal anti-inflammatory drugs in rheumatoid arthritis. BMJ 1998;316:811-8.
6. Laan RF, Jansen TL, van Riel PL. Glucocorticosteroids in the management of rheumatoid arthritis. Rheumatology 1999;38:6-12.
7. van Everdingen AA, Jacobs JW, Siewertsz VRD, Bijlsma JW. 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. Ann Intern Med 2002;136:1-12.
8. Gough AK, Lilley J, Eyre S, Holder RL, Emery P. Generalised bone loss in patients with early rheumatoid arthritis. Lancet 1994; 344:23-7.
9. Sambrook PN, Spector TD, Seeman E, et al. Osteoporosis in rheumatoid arthritis. A monozygotic co-twin control study. Arthritis Rheum 1995;38:806-9.
10. Michel BA, Bloch DA, Wolfe F, Fries JF. Fractures in rheumatoid arthritis: an evaluation of associated risk factors. J Rheumatol 1993;20:1666-9.
11. Adachi JD, Bensen WG, Bianchi F, et al. Vitamin D and calcium in the prevention of corticosteroid induced osteoporosis: a 3 year followup. J Rheumatol 1996;23:995-1000.
12. LoCascio V, Bonucci E, Imbimbo B, et al. Bone loss in response to long-term glucocorticoid therapy. Bone Miner 1990;8:39-51.
13. Adinoff AD, Hollister JR. Steroid-induced fractures and bone loss in patients with asthma. N Engl J Med 1983;309:265-8.
14. Sambrook PN, Eisman JA, Yeates MG, Pocock NA, Eberl S, Champion GD. Osteoporosis in rheumatoid arthritis: safety of low dose corticosteroids. Ann Rheum Dis 1986;45:950-3.
15. Buckley LM, Leib ES, Cartularo KS, Vacek PM, Cooper SM. Effects of low dose corticosteroids on the bone mineral density of patients with rheumatoid arthritis. J Rheumatol 1995;22:1055-9.
16. van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures. J Bone Miner Res 2000;15:993-1000.
17. Laan RF, van Riel PL, van de Putte LB, van Erning LJ, van't Hof MA, Lemmens JA. Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis. A randomized, controlled study. Ann Intern Med 1993;119:963-8.
18. Sambrook P, Raj A, Hunter D, Naganathan V, Mason R, Robinson B. Osteoporosis with low dose corticosteroids: contribution of underlying disease effects and discriminatory ability of ultrasound versus bone densitometry. J Rheumatol 2001;28:1063-7.
19. Eastell R, Reid DM, Compston J, et al. A UK Consensus Group on management of glucocorticoid-induced osteoporosis: an update. J Intern Med 1998;244:271-92.
20. American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. 2001 Update. Arthritis Rheum 2001;44:1496-503.
21. Smith MD, Cheah SP, Taylor K, Ahern MJ. Prevention of corticosteroid induced osteoporosis in inpatients recently discharged from a tertiary teaching hospital. J Rheumatol 2001;28:566-70.
22. Yood RA, Harrold LR, Fish L, et al. Prevention of glucocorticoid-induced osteoporosis: experience in a managed care setting. Arch Intern Med 2001;161:1322-7.
23. Soucy E, Bellamy N, Adachi JD, et al. A Canadian survey on the management of corticosteroid induced osteoporosis by rheumatologists. J Rheumatol 2000;27:1506-12.
24. Hougardy DM, Peterson GM, Bleasel MD, Randall CT. Is enough attention being given to the adverse effects of corticosteroid therapy? J Clin Pharmacol Ther 2000;25:227-34.
25. Peat ID, Healy S, Reid DM, Ralston SH. Steroid induced osteoporosis: an opportunity for prevention? Ann Rheum Dis 1995;54:66-8.
26. Hart DJ, Mootoosamy I, Doyle DV, Spector TD. The relationship between osteoarthritis and osteoporosis in the general population: the Chingford Study. Ann Rheum Dis 1994;53:158-62.
27. van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Oral corticosteroids and fracture risk: relationship to daily and cumulative doses. Rheumatology 2000;39:1383-9.