Osteonecrosis, corticosteroid use and Crohn's disease: Evidence-based medicine versus civil law

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In 1986, a 22-year-old man brought a malpractice action against his physician because he had developed avascular necrosis of both femoral heads. The physician had prescribed prednisone to control the patient's Crohn's disease. Five experts (one in clinical pharmacology, one in orthopedics and three in gastroenterology) testified. The clinical pharmacologist stated that prednisone caused the osteonecrosis, citing the *Compendium of Pharmaceuticals and Specialties* (1), which lists osteonecrosis as an adverse effect of prednisone use. Three gastroenterologists provided a contrary opinion; they had never encountered nor read any reports concerning a link between prednisone and hip necrosis. Neither side referred to any specific, peer-reviewed study to support their respective positions. All testified based on anecdotal evidence. The judge, on a balance of probability, ruled that prednisone probably did cause the hip necrosis (2). An appeal to the Supreme Court was denied.

The court reached its conclusion based on the evidence presented. In general, the obligation of the court is to weigh the evidence and decide on the basis of a balance of probabilities. In the final decision, one position must carry the day. In this case (2), the court preferred the evidence submitted by the plaintiff rather than that of the gastroenterologists. A precedent was set. Subsequent cases (3,4) had similar splits in evidence; orthopedic evidence implicated prednisone as a risk factor for osteonecrosis, while gastroenterological testimony denied such a link. As recently as February 1999, the courts deemed that hip necrosis was caused by the wrongful use of prednisone (5). However, no specific study has ever presented evidence. Based on the ear-

lier, judicially 'accepted' and 'proven' link between prednisone and hip necrosis, plus one publication that identified prednisone as a risk factor (6), the judge ruled that the hip disease was caused by prednisone, stating that "There is no question in this case that the defendant (physician) was aware that the high level, long term use of prednisone would put a patient at risk of developing avascular necrosis of the major bone"(5). Precedent had been set by the 1988 judgement (2), at least in Canada. In subsequent cases, the expert medical testimony suggesting a possible link between osteonecrosis and prednisone use, plus a history of court rulings on the association, have resulted in courts choosing to not re-evaluate their position. The judicial test is not high (50.1%).

Osteonecrosis (aseptic necrosis or avascular necrosis) is characterized by the death of all cellular elements of bone under the cartilage, leading to collapse and fragmentation of the overlying articular cartilage (7). The result is joint degeneration and arthritis. The blood supply to certain bony sites, particularly the femoral head, has a limited collateral circulation. Four mechanisms may be responsible for interrupting this tenuous vascular supply: mechanical disruption from trauma or minor events such as fatigue fractures; thrombosis and embolism from circulating fat or abnormal red blood cells (eg, sickle cell disease); arterial damage from vasculitis or from high pressure within the bone matrix due to excessive packing with fat or cellular elements; and venous occlusion. Once considered an uncommon complication of femoral neck fractures, osteonecrosis is now frequently recognized, accounting for over 10% of total hip replacements.

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Nontraumatic causes of osteonecrosis in adults result from stress or fatigue factors, connective tissue disorders (rheumatoid arthritis, systemic lupus, arthritis or vasculitis), hemoglobinopathy, coagulation disorders, pregnancy, alcohol abuse and others (8). In many of these conditions, the frequency and pathogenesis of osteonecrosis are not well established.

For some time, osteonecrosis appeared to be associated with corticosteroid use. This association is based on a higher prevalence in organ transplantation (5% to 25%), systemic lupus (10%) and chemotherapy (5% to 10%) than would be expected in the general patient population (8). In other conditions treated with corticosteroids, the prevalence of osteonecrosis was too low to indicate an association with confidence. The importance of the underlying disease, relative to the causation of this significant bone complication, has been emphasized only recently (9). Curiously, osteonecrosis is rare in some disease states despite corticosteroid use, either chronically such as the therapy used with rheumatoid arthritis or as a short term, high dosage treatment such as that used for cerebral edema after head injury. That osteonecrosis can even develop after a single, very low dose of steroids indicates its erratic pattern of occurrence.

Osteonecrosis has rarely been reported in patients with inflammatory bowel disease, either during or after corticosteroid use. By 1985, there had been only two case reports in patients with inflammatory bowel disease on steroids – one adult patient and three children (10). The authors attributed the bone changes to either Crohn's disease per se or a combined effect of intravenous lipid use in parenteral nutrition plus corticosteroids. In 1989, a definitive study (6) described a series of patients with inflammatory bowel disease taking corticosteroids who developed osteonecrosis. In this report, the frequency of osteonecrosis was relatively high, affecting seven of 204 consecutive patients with inflammatory bowel disease. Two patients had Crohn's disease, and the rest ulcerative colitis. In a subsequent report, however, none of 55 patients on alternate-day prednisone experienced osteonecrosis (11).

In the present issue of *The Canadian Journal of Gastroenterology*, Freeman and Freeman (pages 138-143) present a review of 877 patients with Crohn's disease followed over 20 years. Four developed osteonecrosis – two had received corticosteroids plus parenteral nutrition (12), and the other two had not experienced either treatment. Even hyperlipidemia associated with intravenous lipid can be a risk factor (10,12). Clearly, patients with Crohn's disease can develop osteonecrosis of the hips in the absence of any history of corticosteroid use, as reported earlier by Freeman and Kwan (13). Crohn's disease may cause vasculitis, which leads to vascular occlusion, further restricting the limited blood supply. Given the frequent use of corticosteroids in patients with inflammatory bowel disease, the rarity of published reports describing osteonecrosis in such patients with this disorder may reflect either an extremely low risk or a disincentive to publish reports of an adverse drug effect. There may also be a detection bias in the older retrospective studies because

magnetic resonance imaging is now recognized to be the most sensitive indicator.

The development of osteonecrosis in inflammatory bowel disease appears, at least in one report, to be associated with a considerably lower accumulative lifetime dose of corticosteroids and a shorter duration of therapy than in other disease states associated with osteonecrosis – 7 g in one series of patients with inflammatory bowel disease (6) versus a 45 g accumulative dose in patients with lupus who developed steroid-associated osteonecrosis (14). In conditions other than inflammatory bowel disease, reports have variably indicated that osteonecrosis may develop with a high initial prednisone dose (15), a high accumulative prednisone dose (16) or a high peak prednisone dose (14). Others have shown no association with the duration of therapy, peak dose or accumulative dose (17).

Evidence-based medicine cannot give credence to a firm association between corticosteroid use for inflammatory bowel disease and osteonecrosis. The association may simply represent a chance occurrence of osteonecrosis in these patients, who commonly receive this prescribed drug, leading to publication of articles on this topic. Conversely, osteonecrosis may occur in patients treated with corticosteroids as a drug complication, a complication of the disease process or both (7,8). Its occurrence in inflammatory conditions without steroid use (12,13,18) supports the notion of disease predisposition.

There is no solid medical evidence that corticosteroids reproducibly cause osteonecrosis in Crohn's disease. At best, this agent contributes to the event. Nevertheless, case reports (not necessarily as peer-reviewed papers in medical literature) have led the pharmaceutical industry to list this as a potential complication of corticosteroid use dating back to 1985 in the *Compendium of Pharmaceuticals and Specialties* (1) and to 1983 in its American counterpart, the *Physicians' Desk Reference* (19). Drug companies presumably had identified one or more case reports and, therefore, listed osteonecrosis as a potential adverse effect.

The legal decisions ruling that steroids, on a simple balance of probability, cause osteonecrosis are based on tenuous medical information that suggests a causal connection between steroids and osteonecrosis. The fact that the risk is not epidemiologically evident in Crohn's disease and has not been established suggests that the risk is not material; its formability can at best be a matter of conjecture and speculation. Nevertheless, because of successful litigation, most practising gastroenterologists provide their patients with this information, helping them to make an intelligent decision. In Canada, there have been at least 10 lawsuits related to steroid use in inflammatory bowel disease since 1990. The risk of legal action against gastroenterologists has more than doubled since the 1980s, with expensive lawsuits running to \$1 million. The potential adverse effect of this association is even included in a suggested information form provided by this journal (20). There is a message for everyone: obtain fully informed consent and seek alternative management schemes for those who appear to be steroid-dependent. Con-

versely, the legal community needs to be aware that any causal relationship is presumptive and not clearly established.

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