# Short-term Corticosteroids and Avascular Necrosis: Medical and Legal Realities

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*Short-term corticosteroids (CSs), most commonly defined as short-term prednisone (STP) 40 to 60 mg or its equivalent, either tapered or level, prescribed over a few days to 3 weeks (total dose, 400–600 mg), often are used to treat acute and self-limiting diseases. Serious side effects, though uncommon, can occur; however, they receive little attention.*

*The literature contains scattered case reports and legal cases that highlight the relationship between STP and avascular necrosis (AVN). The orthopedic literature finds that CSs are one of the most common causes of AVN. An Internet search of AVN identifies several commercial pages prepared for lawyers that describe references and supplies relevant to initiating lawsuits. Court cases consistently find that patients must be informed of treatment risks and options. Informed consent and thorough documentation are required when prescribing STP.*

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Corticosteroids (CSs) affect every body system and long-term use is associated with a myriad of well-established side effects, including avascular necrosis (AVN).[1-6] In contrast, short-term CSs, more commonly described as short-term prednisone (STP), generally are considered to be safe and commonly are recommended for the treatment of severe and acute self-limiting inflammatory conditions such as asthma, drug reactions, contact dermatitis, severe eczema flares, severe urticaria, allergies, bowel disorders, and arthritis. STP refers to the standard starting dose of 40 to 60 mg of prednisone or its equivalent, either tapered or level, prescribed over a few days to 3 weeks. Total dose is up to 600 mg, with most total doses being 400 mg or less.[1-10]

A small number of textbooks discuss the possible relationship between STP and AVN.[11,12] However, there have been case reports and legal cases (including a lawsuit against the author that was dismissed) that associated the use of STP with the subsequent development of AVN.[13,14] To identify the potential risks of STP, a review was conducted of standard textbooks and MEDLINE peer-review publications. Because there was some discordance, further information was obtained from a questionnaire completed by 200 physicians at North York General Hospital, Toronto, Ontario, Canada, and by feedback obtained from an additional 100 physicians during a presentation of this material at the American Academy of Dermatology. Two physicians from the latter group had observed AVN with STP.

## Avascular Necrosis

AVN also is called osteonecrosis, ischemic necrosis, or aseptic necrosis. The common denominator is ischemia that leads to necrosis. More than 90% of cases involve the femoral head of the hip, and 40% to 80% of cases are bilateral.[15-18] Any bone may be involved, including the knee, shoulder, and ankle. Most nontraumatic AVN occurs in patients aged 30 to 50 years, with the average age being 38 years; more men than women are affected (ratio, 8:1–4:1). AVN is a serious disease, with most patients becoming incapacitated and eventually requiring hip replacement because of severe osteoarthritis. Young patients with this condition are disadvantaged because hip replacements have a limited life span (average, 15 years). AVN is present before symptoms develop;

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its earliest detection is by magnetic resonance imaging. Subsequently, the affected joint develops pain and aching that becomes worse with activity and subsides with rest. Femoral neck pain is felt most frequently in the groin. The development of AVN tends to be slow and intermittent, with variable progression. The initial treatment is avoidance of weight bearing, which may delay the progress of the condition, but no treatment arrests AVN. Temporizing treatments include core depression, bone grafting, vascularized fibular bone grafting, osteotomy, and transtrochanteric rotational osteotomy; however, most patients eventually require hip replacement.[15-18] A prospective open-label study suggested that alendronate, a bisphosphonate, was useful in the treatment of early AVN of the hip.[19] Confirmatory studies are required. In rare instances, symptomatic AVN does not progress. Some asymptomatic cases detected by magnetic resonance imaging have cleared spontaneously.[20]

The genesis of nontraumatic AVN often is obscure. In about one third of cases, the condition appears to develop spontaneously, and it is suggested that these cases may have genetic mutations that lead to hypercoagulability.[17] Common nontraumatic associations include CSs, excessive alcohol use, connective tissue diseases (mostly lupus erythematosus), hemoglobinopathies (sickle cell disease), hyperlipidemia, liver disease, renal and heart transplants, cancer, cerebral trauma, radiation treatment, chemotherapy, Crohn disease, Gaucher disease, and caisson disease. Orthopedic literature sources generally list previous CS use as the most common known cause of nontraumatic AVN.[12,15,17,18] A literature review of nontraumatic AVN by Mont and Hungerford[18] found that most cases of AVN were related to CS use and/or excess alcohol intake. Most authors believe that AVN is multifactorial, and there appears to be idiosyncratic susceptibility because only a small number of patients at risk eventually acquire AVN. [12,15-18] Damage to fine blood vessels and subsequent ischemia can result from luminal, intramural, extramural, or mixed damage. (Thrombosis and embolism may develop in patients with alcoholism, liver disease, and hyperlipidemia. Immune complexes may develop in collagen disease and Crohn disease. Cancer, radiation, and chemotherapy may damage blood vessels. Any cell increase within the rigid bone marrow may compress blood vessels, leading to intraosseous hypertension and ischemia, as occurs with cancer and Gaucher disease and with the probable fat deposition and hyperlipidemia induced by CS therapy.[16]

## CSs and AVN

AVN rarely has been reported to occur with endogenous Cushing syndrome.[16] It often is impossible to differentiate the effects of CSs from those of the underlying condition(s) for which it was prescribed. We lack precise knowledge of the importance of factors such as dose, duration of therapy, peak dose, route of administration, cumulative dose, or idiosyncratic susceptibility.[15-18,21,22] The association of AVN with long-term CSs was first reported in Italy in 1957.[23] By 1971, Fisher and Bickel[24] were able to present a clinical study of 77 patients with CS-induced AVN and were able to review an additional 175 cases from the literature. They determined that the common factor was treatment with CSs in doses greater than physiologic replacement for long periods, either continuously or intermittently.[24]

The epidemiologic evidence relating CSs and AVN is confusing. Freeman and Freeman[25] followed 877 patients with Crohn disease, with a mean follow-up of 7.8 years. AVN developed in 4 of 385 men studied. Two of these patients had received CSs and 2 had not. The authors concluded that AVN was a rare complication of Crohn disease, independent of CSs.[25] However, Klingenstein et al[26] conducted a study of inflammatory bowel disease in patients treated with CSs and identified 23 patients with AVN. The authors concluded that inflammatory bowel disease predisposed patients to CS-induced AVN. Threshold doses were not identified, but the mean cumulative lifetime dose for most patients was about 10,000 mg.[26] Gladman et al[27] studied the predictive factors for symptomatic AVN in 744 patients with systemic lupus erythematosus from 1970 to 1995. Symptomatic AVN was found in 12.8% of patients, all had taken CSs. The authors concluded that CSs play a major role in the development of AVN in patients with systemic lupus erythematosus.[26] CSs are used in transplantation, and the incidence of AVN ranges from 5% to 25% after renal and cardiac transplantation.[28] In contrast, Horiuchi et al[29] did not detect any cases of AVN in 169 patients who underwent liver transplantation. Another study observed that the advent of other drugs to replace CSs in immunosuppressive therapeutic regimens after transplantations led to a reduction in AVN.[28] Ce et al[30] studied 33 patients with multiple sclerosis who had received cumulative pulse CS doses of 10 to 15 g. Five patients (15.2%) developed AVN; AVN did not develop in the 27 patients with multiple sclerosis who had not received CSs.[30]

Wang et al[31] fed CSs to chickens and found that the agent produced adipogenesis in the bone marrow. The new fat production caused intraosseous hypertension, which decreased blood flow, leading

to ischemia and subsequent AVN. The production of osteoblasts was reduced, which led to insufficient bone remodeling and poor repair of necrotic bone. The CS effects mostly were reduced by simultaneous treatment with lovastatin.[31] Pritchett[32] studied 284 patients who were already taking statins and were later given high doses of CSs. After an average of 7.5 years, only 1% of patients developed AVN, whereas the expected development was 3% to 20%.[32] Drescher et al[33] injected megadose methylprednisolone into pigs and found that the blood flow of the femoral head epiphysis and metaphyseal cancellous bone was substantially reduced after 24 hours.

Investigations have suggested that steroid-induced apoptosis may play a role in the pathogenesis of AVN. Zalavras et al[34] noted that AVN is associated with osteoblast and osteocyte apoptosis, which they believed was emerging as a potential primary pathogenic mechanism. Ischemia may be a concomitant factor.[34] Calder et al[35] confirmed the steroid-induced widespread apoptosis of osteoblasts and osteocytes and suggested that the process of cell death may involve the activation of inducible nitric oxide synthase, which leads to locally toxic levels of nitric oxide in osteoblasts and osteocytes.

Conventional wisdom has indicated that a 2000-mg cumulative dose of prednisone (or its equivalent) was required for the development of AVN.[16] However, in 1982, Anderton and Helm[36] reported the case of an apparently healthy 23-year-old man with shoulder AVN who had received oral dexamethasone in a dosage of 4 mg every 6 hours for a week (equivalent to 700 mg of prednisolone) 2 years prior for increased intracranial pressure. The authors considered this to be one of the shortest courses of steroid therapy that resulted in AVN,[36] and their review of the literature revealed a previous report in which a patient had received a cumulative dose of only 480 mg of prednisolone.[24] In 1984, Taylor[37] reported 3 male patients aged 45 years and younger who received dexamethasone for neurologic problems. Their cumulative prednisone equivalents ranged from 500 to 1900 mg and they all required a hip replacement. The author's review noted only 4 other cases of multifocal AVN after STP.[37] Sporadic case reports of STP-associated AVN continued to appear, but most cases involved a more than 1000-mg cumulative dose of prednisone or its equivalent, as in the case of the 2 male patients presented by Skinner et al[38] who developed femoral AVN after receiving a 1600-mg cumulative dose of prednisone for infertility treatment.

The first large series that associated AVN with STP was presented by orthopedic surgeons McKee et al[13] in 2001. They reported 15 men with femoral AVN who ranged in age from 20 to 41 years. The mean steroid dose in prednisone equivalents was 850 mg (range, 290–3300 mg). The mean duration of therapy was 20.5 days (range, 7–39 days). The mean time from the administration of CSs to the development of hip symptoms was 16.6 months (range, 6–33 months). Three patients (aged 26, 32, and 35 years) had been treated for poison ivy with total prednisone doses ranging from 290 to 660 mg. The patient receiving 290 mg reported heavy alcohol intake; no medical conditions were present in the other patients. All patients required surgery. The authors concluded that there was strong presumptive evidence that association existed between AVN and CS treatment.[13] In 2006, McKee reported over 100 cases of femoral AVN (oral communication, December 2006). Wong et al[14] studied 1352 neurosurgical patients given short-duration high-dose dexamethasone treatment and observed 4 cases (0.3%) of AVN of the femoral head. The authors advised minimizing the dose and duration of CS treatment.[14]

The interval between CS treatment and the development of symptomatic AVN usually is 6 months to 1 year, but it can be less or rarely up to 3 years or more.[15-18,21,22] However, magnetic resonance imaging studies of patients receiving CSs have indicated that asymptomatic AVN usually begins from 1 to 16 months, with a mean duration of 5.3 months.[39] In a similar study, Oinuma et al[40] found that AVN lesions were detected at 3.1 months on average; they were not found in any patients after 6 months. Long-term follow-up reports were not provided in these papers.

Fisher[41] noted the absence of reports associating the occurrence of AVN with intramuscular steroids. He observed that the effect of intramuscular triamcinolone acetonide lasted 3 to 6 weeks, but the total steroid doses were lower than with oral STP.[41] Subsequently, however, Nasser and Ewan[42] reported a case of AVN that developed in a 42-year-old man who had received annual injections of intramuscular steroids for 11 years for severe hay fever. The lower number of reported cases that associated intramuscular CSs with AVN may be a reflection of the lower use of intramuscular steroids compared with oral steroids rather than a true physiologic difference. Epidemiologic and experimental evidence suggest that the effects of CSs are cumulative, which may account for the increased reported incidence of AVN with repeated courses of STP and with the

case of intramuscular-associated AVN reported by Nasser and Ewan.[42] Sporadic cases of AVN associated with the long-term heavy-dose use of topical CSs were reported and reviewed by Kubo et al[43] in 2001. This association must be rare in view of the millions of treatment days of topical steroids worldwide. The association of AVN with intra-articular CSs and nasal spray CSs also has been infrequently reported.[44-46]

It is important to highlight the distinction between osteonecrosis and osteoporosis. CSs inhibit calcium intestinal absorption and increase renal calcium excretion. They inhibit osteoblast activity and increase osteoclast activity. Therefore, there is a reduction in bone density, which can lead to osteoporotic fractures but not the ischemic necrosis of AVN.[47-49]

## Legal Realities

The relationship between STP (as well as long-term prednisone) and AVN is scientifically controversial, but the references cited indicate that there is substantial evidence to explain their association. The orthopedic literature indicates that CSs are one of the most common causes of AVN, and orthopedic surgeons usually say so when they are called on to serve as expert witnesses. A search for AVN on the Internet will lead to commercial pages prepared for lawyers that outline the relationship between CSs and AVN, giving appropriate references and supplies relevant to initiating lawsuits. Crane[50] noted that long-term CS use, which produces AVN, was the third highest medication involved in malpractice claims in all specialties. The Canadian Medical Protective Association has had a 46% unfavorable legal outcome in cases involving CSs and AVN. AVN is a legally recognized complication of CS therapy (oral communication, November 2006).

Courts are consistent in stating that patients must be informed of treatment risks and options. Failure to inform patients of the material risk of AVN was the major issue in most lawsuits that involved CSs (Canadian Medical Protective Association, oral communication, November 2006).

Failure to inform patients of the material risk of AVN was the major issue in most lawsuits involving CSs and I was sued for this reason. A man with severe poison ivy presented to me and I placed him on prednisone 40 mg, tapered to zero over 3 weeks, with a total cumulative dose of 400 mg. This treatment was repeated by another physician one year later. Three years later, the patient developed hip pain and had a hip replacement the next year. He sued on the basis that he was not informed about the risks, but the case was dismissed because the judge stated that it was not incumbent upon physicians at that time to inform patients of this material risk. It is now.

## Risk Management

Patients given STP must be informed of all material risks and treatment options, and thorough chart documentation is required. The indications for CS use and dose levels must be sound, and the medical records should clearly document the severity of the illness and the weighing of treatment alternatives. The patient must be monitored and the medical record should indicate that CSs were used in the lowest dose and for the shortest time possible. A review of the literature did not identify any serious problems resulting from the use of STP for less than a week as long as there were no specific contraindications against their use and daily doses did not exceed 40 mg. Psychiatric problems are the one possible exception.[51] A cumulative flow sheet should be maintained and prescription renewals must be justified. Patients should be asked (and warned) about receiving additional CSs from other physicians (CS side effects can be cumulative). Disease associations such as excessive alcohol use, sickle cell disease, connective tissue disease, and trauma should be noted. Clinicians should listen carefully to any patient symptoms that might indicate AVN problems.

There are several avenues to informed consent, but the most appropriate is a dialogue between physician and patient, with physician documentation of the discussion in the patient's medical chart. A consent form does not replace this process, but some physicians believe it serves as a memory jog for both themselves and their patients. Informed consent forms promote a logical complete discussion and establish consistent documentation. If a consent form is used, the patient's signed copy should be in his/her medical chart and the other copy should be given to the patient.

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