Corticosteroid-induced osteoporosis and fractures

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Summary

Corticosteroids can cause fractures by reducing bone formation and the viability of osteoblasts and osteocytes. The heightened fracture risk is dose dependent and occurs within months of starting therapy. Daily doses of more than 2.5 mg prednisolone or equivalent are associated with a higher fracture risk. Randomised studies reveal adverse skeletal effects with daily doses as low as 5 mg. After treatment stops, the fracture risk rapidly falls towards baseline unless the patient was taking long-term therapy. Patients who start corticosteroid therapy should routinely receive calcium and vitamin D supplementation. Those with a higher risk of fracture should also be offered a bisphosphonate. Repeated efforts should be made to reduce the dose of corticosteroids or discontinue long-term therapy if possible.

Key words: bisphosphonates, bone, vitamin D.

Introduction

Fragility fractures are a serious complication of long-term treatment with corticosteroids. The high frequency and rapid onset of corticosteroid-related fractures necessitates prompt identification of at-risk patients. A meta-analysis of more than 42 000 patients compared outcomes for patients who had taken oral corticosteroids with those who had not. The relative risk for osteoporotic fracture was 2.63 at the age of 50 and 1.71 at 85 years. For hip fracture the respective relative risks were 4.42 and 2.48. Overall, the reported fracture risk was similar in men and women, independent of prior fracture, and only partially explained by losses in bone mineral density.1

Mechanisms

Bone loss is usually higher at skeletal sites rich in trabecular bone, particularly the vertebral bodies, ribs and distal radius, but it also occurs in cortical bone in the upper femur. The mechanisms of increased bone fragility are not completely understood, but the inhibitory effects of corticosteroids on osteoblasts are likely to be critical. Corticosteroids inhibit replenishment of osteoblasts, reduce the synthesis of bone collagen and osteocalcin by existing osteoblasts, and promote osteoblast and osteocyte apoptosis. Osteoblast inhibition leads to a reduction in the amount of bone replaced in each remodelling cycle. However, the role of osteoclastic bone resorption in fracture risk is less certain as study results have been inconsistent and markers of bone resorption are often unchanged during short-term corticosteroid treatment.

Corticosteroids reduce intestinal calcium absorption and increase renal calcium excretion. This may contribute to hyperparathyroidism and bone loss. These negative effects on calcium balance can be reversed with oral calcium and vitamin D₃ supplementation, or by treatment with active vitamin D metabolites such as 1,25-dihydroxyvitamin D₃ (calcitriol). In some patients, corticosteroids also reduce gonadal function, which may further contribute to bone fragility.

The role of steroid-induced myopathy on fractures is unknown. The increase over time of both vertebral and non-vertebral fractures without an increase in forearm fractures suggests that the direct effects of corticosteroids on bone strength predominate over any effects on falls.

Effects of dosage and timing

Short-term studies show that daily doses of prednisolone as low as 5 mg cause markers of bone formation (for example osteocalcin) to fall rapidly. Both the daily dose and treatment duration, and therefore cumulative dose, are considered responsible for the skeletal adverse effects. However, as

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fractures often occur rapidly after starting corticosteroids, the effects on fractures are probably more closely related to the daily dose rather than to the duration of therapy or cumulative dose.

When high doses (prednisolone > 20 mg/day or equivalent) are used, the annual rate of loss of spinal bone density is 5–15%. The rate of bone loss is most marked in the first six months after starting corticosteroids and can be as high as 27%. Bone loss may slow irrespective of whether or not the dose is tapered as the patient’s underlying condition improves. The relationship of dose to fracture risk and bone mineral density is different. The daily dose is the single most important determinant of fracture, whereas there is a strong inverse relation between cumulative dose and bone mineral density. Patients with high cumulative doses (more than 10 g prednisolone equivalent) show marked deterioration in trabecular micro-architecture characterised by thinning and loss of connectivity, compared to short-term treatment. Hence, fracture risk reduction after withdrawal of corticosteroids is less certain after long-term therapy than after short-term therapy.

In contrast to premenopausal women, people aged over 50 years and postmenopausal women are more susceptible to osteoporosis even with low doses (prednisolone < 7.5 mg/day or equivalent). At doses greater than 20 mg/day, corticosteroids have a devastating effect on bone mineral density irrespective of age, gender or menopausal status. At high doses, trabecular bone connectivity (not merely thickness) is severely compromised, leading to vertebral fractures. Intermittent oral corticosteroids (in men) and inhaled corticosteroids increase vertebral fracture risk, but patients taking intermittent corticosteroids are less likely to sustain fractures than those taking continuous therapy. Taking corticosteroids on alternate days may preserve growth in children, but does not prevent bone loss in children, or in adults. Pulsed intravenous high dose corticosteroids (that is 1 g methylprednisolone) are less deleterious to bone mineral density, but increase the risk of osteonecrosis. The rapid reduction in systemic inflammation after pulsed therapy might be protective, as the underlying diseases for which corticosteroids are prescribed (for example rheumatoid arthritis, Crohn’s disease) often contribute to the increased risk of fractures, independently of corticosteroid therapy.

**Risk assessment**

Each patient’s risk factors should be carefully appraised before prescribing corticosteroids (Fig. 1). Readily identified factors that influence bone loss and fracture risk include the dose, the underlying condition, and factors such as age, female gender, menopausal status and low bone mineral density. In practice, postmenopausal women are those at highest risk for corticosteroid-induced osteoporosis.

The effects of corticosteroids on bone mineral density can be measured precisely and accurately using dual energy X-ray absorptiometry. Early changes are seen in the lumbar spine. Dual energy X-ray absorptiometry of the lumbar spine and femoral neck is recommended for all patients starting long-term (> 3 months) corticosteroids. Repeated measurements at 1–2 year intervals are recommended to monitor bone loss. The T-score can help guide management, but there is no consensus on an appropriate or cost-effective threshold for intervention in patients taking corticosteroids. T-scores of less than –1.0 (USA) or less than –1.5 (UK) have been suggested. The use of these low intervention thresholds in oral corticosteroid users reflects the fact that fracture rates are considerably higher in corticosteroid users than in non-users.

Determining the absolute fracture risk for individual patients is difficult. Scoring systems to ascertain this risk are now emerging, but are not yet in routine use. In one study, a woman aged 65 years with rheumatoid arthritis, low body mass index, and a previous history of fracture and falls who took 15 mg prednisolone daily had a five-year fracture risk of 47% compared with a man with a similar history whose risk was 30.1%.

**Management**

The importance of reducing or stopping corticosteroids, whenever possible, cannot be overemphasised. The general practice research database study reported that the excess risk of fracture diminished within one year of stopping therapy and this was most obvious for vertebral fractures. The risk of hip fracture also fell towards baseline levels after treatment stopped. There are sparse data on the effects of lifestyle interventions in patients using oral corticosteroids. Patients should be advised not to smoke or abuse alcohol. Although proximal muscle weakness is a complication of oral corticosteroids, the possible effects of physical exercise on muscle mass or fracture rates have not been systematically evaluated.

**Calcium and vitamin D**

Calcium alone is insufficient to prevent rapid bone loss in patients starting corticosteroids. However, calcium and vitamin D₂ (cholecalciferol) may blunt the continuing loss during long-term use of corticosteroids. A Cochrane meta-analysis compared patients taking calcium and vitamin D₂ to patients using calcium alone or placebo. The studies were underpowered to detect statistically significant reductions in fracture risk, but revealed a trend towards a lower risk of fracture in patients treated with calcium and vitamin D₂. All patients starting oral corticosteroid therapy are advised to take calcium (1000 mg/day) and
vitamin D₃ (at least 500 IU/day). In practice, the aim should be to maintain serum 25-hydroxyvitamin D₃ levels greater than 50 ng/mL to prevent secondary hyperparathyroidism.

In addition to vitamin D₃, randomised controlled trials demonstrated that the hydroxylated derivatives of vitamin D₃, for example 25-hydroxyvitamin D₃ (calcidiol), 1-hydroxyvitamin D₃ (alfacalcidol) or 1,25-dihydroxyvitamin D₃ (calcitriol) administered together with calcium, were superior to calcium alone in reducing bone loss after corticosteroid therapy (Table 1). The risk of hypercalciuria or hypercalcaemia is higher with the hydroxylated vitamin D₃ metabolites than with plain vitamin D₃, especially when combined with calcium, and this must be monitored. Apart from calcitriol, vitamin D metabolites are not routinely available to Australian prescribers. Studies comparing the vitamin D metabolites in corticosteroid users have not been reported. Alendronate (10 mg/day) is more effective than alfacalcidol (1 microgram/day) in the prevention of corticosteroid-induced bone loss.⁷ However, calcitriol is at least as effective as alendronate in preventing bone loss in corticosteroid users.⁸

**Antiresorptive drugs**

Although the effects of corticosteroids on bone formation predominate, antiresorptive drugs appear to reduce fracture risk both by reducing their effects on osteoclast-mediated bone remodelling and preventing the negative effects of corticosteroids on osteoblast and osteocyte viability. The active metabolites of vitamin D₃, such as calcitriol (0.25–0.5 microgram/day), may effectively slow the rapid bone loss in patients starting corticosteroids. Bisphosphonates, such as alendronate and risedronate, also prevent bone loss in these patients and in those already taking chronic therapy.

A meta-analysis attempted to rank various antiresorptive drugs according to their effect on bone mineral density. It found that bisphosphonates had greater efficacy than no therapy or

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**Table 1**

<table>
<thead>
<tr>
<th>Vitamin D derivative</th>
<th>Dose range</th>
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<tbody>
<tr>
<td>Cholecalciferol (vitamin D₃)¹¹</td>
<td>500 IU/day–100 000 IU/week</td>
</tr>
<tr>
<td>Calcidiol (25-hydroxyvitamin D₃)¹² *</td>
<td>35–40 microgram/day</td>
</tr>
<tr>
<td>Alfacalcidol (1-hydroxyvitamin D₃)¹³ *</td>
<td>0.5–1.0 microgram/day</td>
</tr>
<tr>
<td>Calcitriol (1,25-dihydroxyvitamin D₃)¹⁴</td>
<td>0.5–1.0 microgram/day</td>
</tr>
</tbody>
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* not generally available in Australia
calcium (4.6% difference in percent change in the bone mineral density of the lumbar spine after one year). The efficacy of bisphosphonates was also enhanced when used in combination with vitamin D₃ (6% difference in bone mineral density). ⁸

While bisphosphonates are currently the most effective therapies for the management of corticosteroid-induced osteoporosis, few studies have measured fracture outcomes. The overall reduction in risk of morphometric (X-ray detected) vertebral fractures with bisphosphonates, such as risedronate, is approximately 37%, but there are no efficacy data about hip and other non-vertebral fractures in patients taking corticosteroids. The assumption is that the efficacy is similar to the 30–50% reduction in non-vertebral fractures seen in patients treated for postmenopausal osteoporosis, although this has not been rigorously tested. Further, no study has examined symptomatic vertebral fractures or back pain as a primary end point.

The intravenous bisphosphonates (pamidronate and zoledronic acid) are often used in patients who are intolerant of oral bisphosphonates. Zoledronic acid is effective in reducing vertebral and hip fractures in postmenopausal osteoporosis, and randomised studies in corticosteroid users are under way.

**Anabolic drugs**

Intermittent injections of parathyroid hormone have a bone anabolic effect. A randomised clinical trial showed that recombinant human parathyroid hormone injections could override corticosteroid-induced suppression of bone formation and increase bone mass. ¹⁰ However, the precise role and cost-effectiveness of recombinant parathyroid hormone in postmenopausal and corticosteroid-induced osteoporosis has not been defined.

**Recommendations**

Postmenopausal women taking oral corticosteroids have the highest risk of bone loss and vertebral fracture so prophylaxis should be considered. In men and premenopausal women, the decision to intervene is less clear and depends on factors such as the baseline bone mineral density and the anticipated duration and dose of corticosteroid therapy (Fig. 1).

Oral bisphosphonates, such as alendronate and risedronate, are the drugs of choice for primary prevention of corticosteroid-related osteoporosis. Patients who are intolerant of oral bisphosphonates may be offered calcitriol, or intravenous pamidronate or zoledronic acid. Although many patients will not qualify for therapy under the Pharmaceutical Benefits Scheme, they should be offered treatment if considered to be at higher risk of fractures.

While calcium alone is ineffective in preventing osteoporosis in patients starting high-dose corticosteroids, all patients should receive calcium and those on bisphosphonates should take vitamin D.

In patients on long-term low-dose prednisolone (< 7.5 mg/day or equivalent), calcium and vitamin D₃ therapy may be sufficient to prevent continuing bone loss and reduce falls. However, patients who continue to lose bone or those at high risk of fracture (previous fragility fracture, bone density < -1.5) should also be offered oral bisphosphonates. Although most clinical trial data are limited to 1–2 years, it is rational to maintain fracture prophylaxis for as long as corticosteroids are taken at a daily dose of more than 5 mg prednisolone or equivalent.

**References**


New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained either from the manufacturer’s approved product information, a drug information centre or some other appropriate source.

Lenalidomide

Revlimid (Celgene)

5 mg, 10 mg, 15 mg and 25 mg capsules

Approved indication: multiple myeloma

Australian Medicines Handbook section 14.3

Multiple myeloma is a cancer of plasma cells in bone marrow. This disease is characterised by increased levels of paraprotein, an abnormal type of immunoglobulin produced by tumour cells. Multiple myeloma is incurable with conventional treatments and the median survival time after diagnosis is 3–5 years.1 Modern treatments such as bone marrow transplant, bortezomib (Aust Prescr 2006;29:84-7) and thalidomide (Aust Prescr 2003;26:146-51) have improved the prognosis.

Lenalidomide is an analogue of thalidomide. Its mechanism of action is not clearly understood although it is thought to modulate the immune system. It inhibits proliferation of certain haematopoietic tumour cells, prevents the growth of blood vessels within tumours and induces proliferation of specialised immune cells that attack cancerous cells.

Following oral administration in patients with multiple myeloma, lenalidomide is rapidly absorbed and maximum plasma concentrations are reached within 0.5–4 hours. In healthy volunteers, its elimination half-life increases with dose from about three hours with 5 mg up to nine hours with 400 mg. Most of the drug is excreted unchanged in urine. Lenalidomide should be taken at least one hour before or two hours after food.

In studies of multiple myeloma, patient responses are generally judged by changes in concentrations of paraprotein. In an open-label trial, the efficacy of lenalidomide was investigated in patients with relapsed or relapsed and refractory multiple myeloma. Responses were observed in 1 of 5 patients given

10 mg/day lenalidomide, 2 of 3 patients given 25 mg/day and 12 of 13 patients given 50 mg/day.2 In another trial, patients with relapsed or relapsed and refractory multiple myeloma received either 30 mg lenalidomide once daily (67 patients) or 15 mg lenalidomide twice daily (35 patients) for 21 days of a 28-day cycle. Patients with stable or progressive disease after two cycles of treatment had dexamethasone added. Overall, 25% of patients responded to lenalidomide treatment. Four patients had a complete response in the once-daily group, whereas there were no complete responses in the twice-daily group. During the trial, 68 of the 102 patients had dexamethasone added and 20 of these patients responded to the addition. The median progression-free survival time was 7.7 months with the single dose of lenalidomide and 3.9 months with the twice-daily dose.3

In two phase III trials totalling 704 patients with relapsed or refractory multiple myeloma, lenalidomide (25 mg once daily for 21 days of a 28-day cycle) or placebo was added to dexamethasone treatment (40 mg). Results were similar in each trial with more patients taking lenalidomide plus dexamethasone responding to treatment compared to those taking dexamethasone alone (approximately 61% vs 22%). Median time to progression was around 11 months with combination therapy compared to just under 5 months with dexamethasone alone.4,5 Monitoring of complete blood counts is recommended because neutropenia and thrombocytopenia are very common with lenalidomide (especially when used with dexamethasone) and patients often need their dose to be reduced or interrupted. Growth factors may be needed for patients with neutropenia. There is also an increased risk of deep vein thrombosis and pulmonary embolism in patients taking lenalidomide with

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 55)

5. The effectiveness of bisphosphonates in preventing hip fracture in patients taking corticosteroids is unknown.

6. Calcium prevents the rapid loss of bone mineral density in patients starting corticosteroids.