

# Supporting Evidence Document: Prevention of Glucocorticoid-induced Osteoporosis

## Background

The recommendations for adult patients (> 18 years old) found in the BCR GN protocols for reducing the risk of glucocorticoid-induced osteoporosis are based on the 2010 and 2017 American College of Rheumatology (ACR) guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis.<sup>1,2</sup>

Many of the ACR recommendations are conditional, meaning the desirable effects probably outweigh the undesirable ones. Therefore, these recommendations apply to the majority of patients, but not all. As such, conditional recommendations are preference-sensitive and always warrant a shared decision-making approach.

### 1. The role of calcium and vitamin D

Calcium intake of 1000 to 1200 mg/day (supplement plus oral intake) and vitamin D supplementation of 600 to 800 units (supplement plus oral intake) are recommended for all adults taking any dose or duration of glucocorticoid [conditional recommendation].<sup>1,3</sup>

- This recommendation is based on two meta-analyses that found calcium and vitamin D to significantly increase bone mineral density in the lumbar spine and/or forearm after two years.<sup>4,5</sup>
- Although fracture risk was not reduced, both meta-analyses recommended all patients prescribed glucocorticoids be given calcium and vitamin D prophylactic therapy due to their low cost and low risk of toxicity.<sup>4,5</sup>

### 2. The role of bisphosphonates

A bisphosphonate is recommended for the following patient groups taking prednisone > 2.5 mg/day for ≥ 3 months - as long as no contraindications exist [conditional recommendation]:

1. Patients with a history of fragility fracture, or an established diagnosis of osteoporosis.<sup>1</sup>
2. Postmenopausal women and men ≥ 50 years.<sup>2</sup>
3. Patients ≥ 30 years who require an initial prednisone dose ≥ 30 mg/day, and who have received a cumulative prednisone dose > 5 grams in the previous year (e.g. 30 mg daily for 6 months).<sup>1</sup>

### 3. The Fracture Risk Assessment Tool

The latest guidelines from the United States and United Kingdom have moved towards calculating a 10-year probability of fracture to guide bisphosphonate therapy for patients ≥ 40 years old, using the Fracture Risk Assessment (FRAX) tool.<sup>1,6</sup>

Determining a FRAX score may not be pragmatic for many renal teams as it requires information such as history of fragility fracture, age, sex, body mass index, family history of hip fracture, current smoking status, alcohol intake, presence of rheumatoid arthritis, secondary osteoporosis, and bone mineral density (if done).

If FRAX is accurately calculated with glucocorticoid-adjustment (for patients given more

than 7.5 mg/day of prednisone, the FRAX score should be increased by 15% for major osteoporotic fracture and 20% for hip fracture), the following criteria can be used to augment the above 3 recommendations for bisphosphonate therapy:

4. Patients  $\geq$  40 years old with a 10-year probability of major osteoporotic fracture  $\geq$  10%.
5. Patients  $\geq$  40 years old with a 10-year probability of hip fracture  $\geq$  1%.

#### 4. Women of childbearing potential

It is recognized that the above recommendations may lead to increased bisphosphonate use in women of childbearing potential. In these patients, the decision to initiate therapy should be individualized; thus, the following discussion about the risks and benefits of treatment may help facilitate this discussion:

- Glucocorticoid induced osteoporosis should be reversible upon discontinuation of therapy, especially in younger patients (age < 40 years).<sup>1</sup>
- Bisphosphonates are not intended to be used during pregnancy, and should be discontinued as soon as possible prior to a planned pregnancy.<sup>7</sup> After discontinuation, bisphosphonates are gradually released from the bone matrix; this process can take years, which may lead to embryo-fetal bisphosphonate exposure.<sup>8</sup>
- In animal studies, which used higher doses of bisphosphonates than would be used in humans, babies exposed to alendronate during pregnancy had an overall decrease in bone growth compared to controls.<sup>9</sup>
- There are no controlled trials in humans, but over 50 case studies have reported no significant harm in human babies.<sup>10</sup> Transient

asymptomatic hypocalcemia has been described in one newborn whose mother was treated with intravenous pamidronate prior to conception;<sup>11</sup> thus, checking a serum calcium level within the first 24 hours of birth may be considered.

- In patients  $\geq$  30 years who require an initial prednisone dose  $\geq$  30 mg/day, and has received a cumulative prednisone dose > 5 grams in the previous year, the relative risk of clinical osteoporotic fracture is increased by almost 4 fold (RR 3.63, 95% CI 2.54 – 5.2). For this reason the ACR now recommend preventative bisphosphonate therapy in this population, even when there is no history of a fragility fracture or an established diagnosis of osteoporosis.<sup>12</sup>
- In a meta-analysis of 27 studies evaluating bisphosphonate therapy for the prevention of glucocorticoid induced osteoporosis compared to placebo, a 43% relative risk reduction in new vertebral fractures (44 vs. 77 per 1000 persons; RR 0.57, 95% CI 0.35 - 0.91) was found, but there was no significant reduction in nonvertebral fractures (42 vs. 55 per 1000 persons, RR 0.79, 95% CI 0.47 – 1.33).<sup>13</sup>

#### 5. Factors to consider with CKD

Lastly, there are additional factors to consider before prescribing oral bisphosphonates in patients with chronic kidney disease (CKD). They include the following:

- There is growing evidence and experience with using bisphosphonates in patients with CKD and the risk of nephrotoxicity with oral formulations is considered to be negligible; however, there remains no definitive trials in patients with CKD G4 to G5. Consider avoiding bisphosphonates if the eGFR is anticipated to be permanently below 30 ml/min/1.73 m<sup>2</sup> due to the risk of adynamic

bone disease, and lack of proven efficacy and long-term safety data.<sup>14,15</sup>

- Alendronate and risedronate are both approved by Health Canada to be used for prevention of glucocorticoid-induced osteoporosis, but risedronate requires special approval for reimbursement in British Columbia.<sup>7,16</sup>

## References

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