TITLE: Bisphosphonates for the Prevention of Osteoporosis in Patients Treated with Systematic Corticosteroids: A Review of the Clinical Evidence and Guidelines

DATE: 02 August 2011

CONTEXT AND POLICY ISSUES:

Corticosteroids (glucocorticoids) are a class of steroids that have anti-inflammatory and immunosuppressive properties.\(^1\) As such, they are used in the management chronic disorders with an underlying inflammatory component such rheumatoid arthritis, inflammatory bowel disease, and chronic obstructive pulmonary disease and following organ transplantation.\(^2\) Corticosteroid use is associated with bone loss, which can lead to bone fragility and fractures.\(^1,3\) Evidence suggests that individuals who use corticosteroids are at six times the risk of vertebral fractures and twice the risk of hip fracture.\(^1\) Bone loss with corticosteroids begins within the first few months of treatment and can occur even at relatively low dosages (for example, 2.5mg to 7.5 mg of prednisone equivalents daily).\(^3\)

Pharmacological and non-pharmacological measures can be used to prevent corticosteroid-induced bone loss.\(^3\) Non-pharmacological measures include weight-bearing exercises and avoidance of smoking and excess alcohol.\(^3\) Pharmacotherapy may involve the supplementation of vitamin D and calcium, active vitamin D metabolites such as alfalcacidol and calcitriol, and bisphosphonates.\(^1,4\) Bisphosphonates are a class of medications that inhibit osteoclastic bone resorption, thereby increasing bone density and mass. Alendronate, risedronate and etidronate are bisphosphonates that are administered orally and are approved for use in Canada for the prevention of corticosteroid induced osteoporosis.\(^5\) Zoledronic acid is also approved for use in Canada for the prevention of corticosteroid induced osteoporosis and is administered as a once yearly intravenous (IV) infusion. Pamidronate (administered as an IV infusion) and clondronate (administered orally or IV) are also bisphosphonates available in Canada but are not specifically approved for use in the prevention of corticosteroid induced osteoporosis.\(^6-8\)

This report will review the evidence regarding the use of bisphosphonates for the prevention of osteoporosis in patients treated with systemic corticosteroids and guidelines for their optimal duration of use. This information could help inform policy decisions about coverage of bisphosphonates for this specific indication.

Disclaimer: The Rapid Response Service is an information service for those involved in planning and providing health care in Canada. Rapid responses are based on a limited literature search and are not comprehensive, systematic reviews. The intent is to provide a list of sources and a summary of the best evidence on the topic that CADTH could identify using all reasonable efforts within the time allowed. Rapid responses should be considered along with other types of information and health care considerations. The information included in this response is not intended to replace professional medical advice, nor should it be construed as a recommendation for or against the use of a particular health technology. Readers are also cautioned that a lack of good quality evidence does not necessarily mean a lack of effectiveness particularly in the case of new and emerging health technologies, for which little information can be found, but which may in future prove to be effective. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete and up to date, CADTH does not make any guarantee to that effect. CADTH is not liable for any loss or damages resulting from use of the information in the report.

Copyright: This report contains CADTH copyright material. It may be copied and used for non-commercial purposes, provided that attribution is given to CADTH.

Links: This report may contain links to other information available on the websites of third parties on the Internet. CADTH does not have control over the content of such sites. Use of third party sites is governed by the owners’ own terms and conditions.
RESEARCH QUESTIONS:

1) What is the clinical evidence on the use of bisphosphonates for the prevention of osteoporosis in patients treated with systemic corticosteroids?

2) What are the guidelines and recommendations on the optimal duration of bisphosphonates therapy for the prevention of osteoporosis in patients treated with systemic corticosteroids?

KEY MESSAGE:

Evidence from three systematic reviews and seven randomized controlled trials suggested that bisphosphonates prevent bone loss associated with use of oral corticosteroids. However, one systematic review and one randomized controlled trial found that the reduction in non-vertebral fractures with bisphosphonates was not statistically significant.

METHODS:

Literature search strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2011, Issue 6), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 1995 and July 6, 2011.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to the selection criteria presented in Table 1.

Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Adult patients taking systemic corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Bisphosphonates</td>
</tr>
<tr>
<td>Comparator</td>
<td>Not specified</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Q1: Prevention of osteoporosis: osteoporotic fractures and bone mineral density</td>
</tr>
<tr>
<td></td>
<td>Q2: Guidelines and recommendations on the optimal length of treatment</td>
</tr>
<tr>
<td>Study Designs</td>
<td>Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials and guidelines</td>
</tr>
</tbody>
</table>

Exclusion Criteria

Articles that evaluated bisphosphonates in the treatment (rather than prevention) of corticosteroid-induced osteoporosis were excluded, as were duplicate publications of the same study. Studies that were published prior to 1995 or included in the systematic reviews selected for this report were excluded, too.
Critical Appraisal of Individual Studies

The quality of the included systematic reviews was assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool. The adequacy of randomization, allocation concealment, blinding of patients, clinicians or health care providers, data collectors and outcome assessors, and loss to follow-up, early stopping of trial, and description of intention-to-treat analysis were considered in the evaluation of the quality of the included randomized controlled trials (RCTs).

SUMMARY OF EVIDENCE:

Quantity of Research Available

The literature search identified 224 studies, 46 of which were obtained for full-text screening based upon their abstracts and 178 of which were excluded based upon abstracts. For the first research question, ten of these studies (three systematic reviews and seven RCTs) were selected for inclusion in the report. One additional relevant systematic review was identified from the grey literature search for the first research question and was included. Twelve additional relevant RCTs were identified for the first research question, but were included in one or more of the systematic reviews. They, therefore, were not summarized individually in this report. No relevant evidence-based guidelines were identified for the second research question. The study selection process is outlined in a PRISMA flowchart in Appendix 1.

Summary of Study Characteristics

Systematic Reviews

The characteristics of the included systematic reviews are summarized in Appendix 2. The populations of interest in the four systematic reviews included any patients on corticosteroids (i.e., treatment or prevention populations); however, results were presented for subgroups of studies that enrolled patients who were corticosteroid naïve or had began therapy within the previous 90 days (prevention studies). In three reviews, any drug in the bisphosphonate class was an intervention of interest. One review was restricted to etidronate only. One systematic review considered only active treatments as comparators, one considered placebo as the comparator; and one considered only placebo with or without vitamin D as the comparators of interest. In the fourth systematic review, the comparator was not specified. Only RCTs were eligible for inclusion in the four systematic reviews.

Randomized Controlled Trials

The characteristics of the selected RCTs are outlined in Appendix 3. One RCT was conducted in each of the following countries: Germany, China, France, Japan, Netherlands, and Belgium. The seventh RCT was multinational, being conducted in 12 European countries, Australia, Hong Kong, Israel and the United States. All of the included RCTs were described as double-blinded, with the exception of one study, which used an open-label design. The study duration ranged from 90 days to 18 months but was most frequently 12 months. The efficacy of alendronate (oral) was evaluated in one study, clodronate (IV) in one study, pamidronate (IV) in one study, risendronate (oral) in two studies, and zoledronate (IV) in two studies. All studies assessed bone mineral density (BMD) as an outcome, but the incidence of fracture was reported in only three studies.
Summary of Critical Appraisal

Systematic Reviews

The strengths and limitations of the included systematic reviews and RCTs are summarized in Appendix 4. Three of the four included systematic reviews used comprehensive methods to search the literature, but the fourth searched just one database. Three of four systematic reviews included a formal assessment of study quality, but the results of the quality assessment did not appear to be considered when formulating the conclusions. Publication bias was not assessed in any of the included systematic reviews.

Randomized Controlled Trials

The strengths and limitations of the included RCTs also are summarized in Appendix 4. In one study, the method of randomization of participants to each treatment arm was not described. Two studies stated that the allocation sequence was concealed, whereas the other five studies did not. While six of the seven studies were described as double-blind, it was unclear in several studies if clinicians and outcome assessors were blinded. In three studies, the loss to follow-up was greater than 10% of participants in one or both treatment arms. Three studies used an intention-to-treat analysis. The statistical analyses presented in most studies did not include the confidence intervals for the difference in treatment effect between groups. Further, the clinical importance of the difference between groups was not commented on in the RCTs.

Summary of Findings

Clinical evidence on the use of bisphosphonates for the prevention of osteoporosis in patients treated with systemic corticosteroids

Vertebral and Non-vertebral Fractures

In separate systematic reviews, the reduction in relative risk (RR) of vertebral fractures with etidronate was not statistically significant. Both of these estimates were based upon pooled estimates across studies. For ibandronate, pamidronate and risendronate, the reduction in relative risk of vertebral and non-vertebral was not statistically significant. Ibandronate is not available in Canada. Thus, these results may not be applicable to Canada. As well, pamidronate is not approved for use in Canada for the prevention of corticosteroid induced osteoporosis, which again could limit the generalizability of the findings to Canada. The estimates for fracture risk with ibandronate, pamidronate and risendronate were derived from single studies for each drug. In one RCT, the estimated hazard ratio suggested that there was no difference in non-vertebral fractures and new deformity with alendronate compared with alfalcaldol (Appendix 5).

Bone Mineral Density

Changes in BMD with etidronate were reported in three systematic reviews (Appendix 5). In two systematic reviews, pooled estimates suggested statistically significant reductions in loss of BMD in the lumbar spine, trochanter and femoral neck. In the third systematic review data were not pooled. In this systematic review, the change in BMD in the lumbar spine was statistically significant but not statistically significant in the femoral neck in five studies.
clinical significance of the magnitude of the difference between groups was not discussed. Authors of the three systematic reviews that reported change in BMD as an outcome all concluded that bisphosphonates prevented bone loss in patients treated with corticosteroids.\textsuperscript{10-12}

In one systematic review, the difference in decrease in BMD with risendronate was statistically significant in the lumbar spine and trochanter, but not in the femoral neck, relative to control.\textsuperscript{15} It should be noted that this systematic review included one study of risendronate (Appendix 5). In one RCT that compared risendronate with placebo, the change from baseline in lumbar spine BMD favoured risendronate, but there was no difference between the change in BMD in the hip, femoral neck, and femoral trochanter.\textsuperscript{15} In another RCT that compared risendronate alone or in combination with alfacalcidol to alfacalcidol alone, BMD increased from baseline to follow-up with risendronate alone and risendronate in combination with alfacalcidol but decreased with alfacalcidol alone.\textsuperscript{17}

In two RCTs, the increase in BMD from baseline with zoledronate was greater than placebo\textsuperscript{13} or risendronate\textsuperscript{14} for the lumbar spine (Appendix 5). The change in BMD in the trochanter also favoured zoledronate over risendronate; however, for the femoral neck, total hip, and distal radius, the difference was not statistically significant.\textsuperscript{14}

Clodronate was compared with placebo in one RCT.\textsuperscript{16} While the change in BMD in the lumbar spine and femoral neck favoured clodronate over placebo, no statistical analyses were reported.

In an RCT that compared the change in BMD with alendronate to alfacalcidol, alendronate was favoured over alfacalcidol for the lumbar spine and femoral neck but not the total hip.\textsuperscript{21} In a study that compared pamidronate with placebo, BMD increased in the lumbar spine and decreased in the placebo group, but no statistical analysis was reported for the difference.

**Limitations**

No evidence-based guidelines were identified that addressed optimal duration of treatment with bisphosphonates for preventing osteoporosis in patients initiating treatment with corticosteroids. Most of the included systematic reviews and RCTs reported on changes in BMD as an outcome; however, evidence pertaining to fracture risk was limited to one systematic review and one RCT. The majority of evidence from this systematic review related to etidronate, as there was one study that met the inclusion criteria for each of the three other bisphosphonates included in the review. Thus, evidence of efficacy of the other bisphosphonates for the prevention of fracture in patients who are treated corticosteroids is lacking.

The majority of evidence included in this report related to changes in BMD, a surrogate outcome for fracture risk. In most of the included RCTs, participants received a co-intervention with calcium and/or vitamin D. Thus, the results of the included studies and their generalizability should be interpreted with this in mind (i.e. the bisphosphonate was assessed as an “add on” to standard treatment). The included systematic reviews and RCTs had a number of limitations, as outlined previously. In particular, in the majority of studies, it was unclear if the allocation sequence was concealed. Further, the reporting of blinding of clinicians, outcome assessors and data collectors was poor, as was the description of the statistical analyses, making it difficult to determine if an intention-to-treat analysis was performed.
CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

Evidence from systematic reviews and RCTs suggest that bisphosphonates can prevent the bone loss associated with the use of corticosteroids to treat a number of inflammatory conditions. The lumbar spine was the area of the skeleton where a favourable impact on BMD was most consistently observed across studies, regardless of the specific bisphosphonate used. It should be noted that pamidronate, and clordonate are not approved in Canada for the treatment of corticosteroid induced osteoporosis, so use for this indication would be considered ‘off-label’. Evidence regarding the reduction in risk of fracture with bisphosphonates was sparse. The available evidence that was included in this report suggested that the use of bisphosphonates to prevent vertebral and non-vertebral fracture in patients receiving corticosteroids is inconclusive. No evidence-based guidelines were identified that addressed optimal duration of treatment with bisphosphonates for patients initiating treatment with corticosteroids.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca
REFERENCES:


APPENDICES:

APPENDIX 1: Selection of Included Studies

224 citations identified from electronic literature search and screened

178 citations excluded

46 potentially relevant articles retrieved for scrutiny (full text, if available)

48 potentially relevant reports

37 reports excluded:
- irrelevant population (21)
- irrelevant comparator (3)
- already included in at least one of the selected systematic reviews (2)
- other (review articles, editorials) (11)

11 reports included in review
Appendix 2: Characteristics of Included Systematic Reviews

<table>
<thead>
<tr>
<th>First Author, Country, Publication Year</th>
<th>Eligibility Criteria</th>
<th>Included Study Designs</th>
<th>Number of Included Studies</th>
</tr>
</thead>
</table>
| Kanis, 2007 United Kingdom              | Population: patients treated with corticosteroids  
Intervention: bisphosphonates*  
Comparator: SERMs, parathyroid hormone, vitamin D, 1α-hydroxylated derivatives of vitamin D, calcitonin, pharmacological doses of calcium, estrogens and estrogen-like molecules, anabolic steroids, fluoride salts, thiazide diuretics, testosterone  
Outcome: vertebral fracture, non-vertebral fracture, associated beneficial or adverse effects, continuance, compliance  
To be included, studies had to report a fracture incidence as the number of patients sustaining fractures | RCTs | 45 studies in total, nine of which were prevention studies.  
**Prevention Studies**  
Etidronate: 4 studies  
Ibandronate: 1 study  
Pamidronate: 3 studies  
Risendronate: 1 study |
| Blair, 2000 United States              | Population: adults receiving corticosteroids  
Intervention: bisphosphonates  
Comparator: not specified  
Outcome: BMD assessed using DEXA | RCTs | 13 studies in total, 6 of which were prevention studies.  
**Prevention Studies**  
Etidronate: 5 studies  
Risendronate: 1 study |
| Homnik, 2000 Canada                    | Population: Adults with underlying inflammatory disorders, starting treatment with or currently on systemic corticosteroids and who had not received bisphosphonates in the six months before the start of the study.  
Intervention: bisphosphonates alone or in combination with vitamin D  
Comparator: placebo alone or in combination with vitamin D  
Outcome: percent change in BMD in the femoral neck and lumbar spine at one year  
Other inclusion criteria: Adequate description of medication regimen and adequate description of withdrawals and dropouts. Study participants and/or outcome assessors had to be blinded. | RCTs | 13 studies in total, 6 of which were prevention studies.  
**Prevention Studies**  
Etidronate: 6 studies |
| Adachi, 2000 Multiple countries, including Canada | Population: patients in corticosteroids  
Intervention: etidronate  
Comparator: placebo  
Outcome: percent change in BMD and incident fractures | RCTs | 5 studies in total, 3 of which were prevention studies.  
**Prevention Studies**  
Etidronate: 3 studies |

BMD=bone mineral density; DEXA: Dual energy x-ray absorptiometry; RCT=randomized controlled trial; SERM=selective estrogen receptor modulator;  
* Other interventions were also included in the systematic review, but were not relevant to the research questions of this rapid review.
<table>
<thead>
<tr>
<th>First Author, Publication Year, Country</th>
<th>Study Design, Length of Follow-up</th>
<th>Patient Characteristics, Sample Size (n)</th>
<th>Intervention</th>
<th>Comparator(s)</th>
<th>Clinical Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klaus, 2011&lt;sup&gt;13&lt;/sup&gt; Germany</td>
<td>Randomized, double-blind, placebo controlled trial 90 days</td>
<td>Adult patients (n=40) with Crohn's disease who were corticosteroid free for at least three months prior to screening. Corticosteroid dose: Prednisolone 60 mg daily</td>
<td>Single IV dose of 4 mg zoledronate (n=20) 400 mg calcium twice daily and 1000 IU of colecalciferol daily</td>
<td>400 mg calcium twice daily and 1000 IU of colecalciferol daily (n=20)</td>
<td>Change from baseline in BMD of lumbar spine after 90 days</td>
</tr>
<tr>
<td>Reid, 2009&lt;sup&gt;14&lt;/sup&gt; 12 European countries, Australia, Hong Kong, Israel and the United States</td>
<td>Double-blind, double-dummy randomized controlled trial 12 months</td>
<td>Patients aged 18 to 85 expected to receive corticosteroid for at least 12 months. Subgroup of patients who had been taking corticosteroid for less than 3 months (n=288). Could not have received medications for the treatment of osteoporosis. Corticosteroid dose: Prednisolone 7.5 mg daily or equivalent</td>
<td>Single IV dose of 5 mg zoledronate (n=144) 1000 mg elemental calcium and 400 to 1200 IU of vitamin D daily</td>
<td>Oral risendronate 5 mg/day (n=144) 1000 mg elemental calcium and 400 to 1200 IU of vitamin D daily</td>
<td>Change in BMD in the lumbar spine from baseline to 12 months.</td>
</tr>
<tr>
<td>Mok, 2008&lt;sup&gt;15&lt;/sup&gt; China</td>
<td>Randomized, double-blind, placebo controlled trial 6 months</td>
<td>Adult ambulatory patients (n=120) with chronic conditions that required treatment with high-dose corticosteroid for at least 6 weeks. Could not have received medications for the treatment of osteoporosis in the previous 12 months. Corticosteroid dose: ≥ 0.5 mg/kg/day oral prednisolone or equivalent</td>
<td>Oral risendronate 5 mg/day (n=60) 1000 mg of elemental calcium daily</td>
<td>1000 mg of elemental calcium daily (n=60)</td>
<td>Change in BMD in the lumbar spine and hip from baseline to 6 months. New vertebral fractures.</td>
</tr>
<tr>
<td>Abitbol, 2007&lt;sup&gt;16&lt;/sup&gt; France</td>
<td>Randomized, double-blind, placebo controlled trial 12 months</td>
<td>Patients (n=67) aged 20 to 60 years with inflammatory bowel disease starting treatment with corticosteroids. Patients who received corticosteroids in the three months prior to the study or anti-osteoporotic</td>
<td>Clodronate IV infusion 900 mg (n=33) every 3 months 1000 mg elemental calcium and 800 IU of vitamin D daily</td>
<td>1000 mg elemental calcium and 800 IU of vitamin D daily (n=34)</td>
<td>Change in lumbar and femoral BMD from baseline to 12 months Vertebral fractures</td>
</tr>
<tr>
<td>First Author, Publication Year, Country</td>
<td>Study Design, Length of Follow-up</td>
<td>Patient Characteristics, Sample Size (n)</td>
<td>Intervention</td>
<td>Comparator(s)</td>
<td>Clinical Outcomes</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>----------------------------------</td>
<td>------------------------------------------</td>
<td>--------------</td>
<td>---------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Kikuchi, 2007 Japan</td>
<td>Randomized, open-label, controlled trial 12 months</td>
<td>Patients (n=37) with glomerulonephritis who initiated high dose corticosteroid treatment. Corticosteroid dose: 0.6 to 0.8 mg/kg/day oral prednisolone or equivalent</td>
<td>Oral risendronate 2.5 mg per day (n=12) Oral risendronate 2.5 mg per day and 0.5 mcg per day of alfacalcidol (n=11) No calcium supplementation</td>
<td>0.5 mcg per day of alfacalcidol (n=15) No calcium supplementation</td>
<td>Change in BMD of the lumbar spine, total hip, trochanter and distal radius from baseline to 12 months.</td>
</tr>
<tr>
<td>de Nijs, 2006 Netherlands</td>
<td>Double-blind, double dummy, randomized controlled trial 18 months</td>
<td>Patients aged 18 to 90 (n=201) with rheumatic disease who had started treatment with corticosteroids within the previous 12 weeks and were expected to continue for at least 6 months. Patient who had received medications for the treatment of osteoporosis in the prior year were excluded. Corticosteroid dose: Prednisolone 7.5 mg daily or higher (or equivalent)</td>
<td>Oral alendronate 10 mg daily (n=100). Calcium 500 mg and vitamin D 400 IU daily if needed.</td>
<td>Oral alfacalcidol 1 mcg daily (n=101). Calcium 500 mg and vitamin D 400 IU daily if needed.</td>
<td>Change in BMD of the lumbar spine, femoral neck and total hip from baseline to 18 months. New vertebral deformities and fractures. Nonvertebral fractures.</td>
</tr>
<tr>
<td>Van Offel, 2001 Belgium</td>
<td>Randomized, double-blind, placebo controlled trial One year</td>
<td>Patient with rheumatoid arthritis, initiating treatment with prednisone. Patients previously treated with bisphosphonates or corticosteroids were excluded. Corticosteroid dose: Prednisolone 5 to 10 mg daily</td>
<td>Pamidronate 60 mg IV infusion every three months. 1000mg calcium and 5mg folic acid daily. Vitamin D supplementation based on level.</td>
<td>1000 mg calcium and 5 mg folic acid daily. Vitamin D supplementation based on level.</td>
<td>Change in BMD of the lumbar spine, hip and metacarpals from baseline to one year.</td>
</tr>
</tbody>
</table>

BMD=bone mineral density; IU=international unit; IV=intravenous; kg=kilogram; mcg=microgram; mg=milligram;
### Appendix 4: Summary of Study Strengths and Limitations

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systematic Reviews</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Kanis, 2007<sup>20</sup>     | • Comprehensive literature search  
   • Detailed characteristics of the included studies were presented  
   • Formal quality assessment of the included studies  
   • Conflict of interest was stated | • Study selection and data extraction were performed in duplicate  
   • Publication bias was not assessed  
   • Did not consider the results of the quality assessment when formulating conclusions |
| Blair, 2000<sup>10</sup>      | • Comprehensive literature search  
   • Detailed characteristics of the included studies were presented  
   • Formal quality assessment of the included studies | • No list of excluded studies  
   • Publication bias was not assessed  
   • Conflict of interest was not stated  
   • Methods for data extraction unclear  
   • Did not consider the results of the quality assessment when formulating conclusions |
| Homnik, 2000<sup>11</sup>     | • Duplicate study selection and data extraction  
   • Comprehensive literature search  
   • Detailed characteristics of the included studies were presented  
   • Conflict of interest was stated  
   • Formal quality assessment of the included studies | • Publication bias was not assessed  
   • Did not present the results of the quality assessment  
   • Did not consider the results of the quality assessment when formulating conclusions |
| Adachi, 2000<sup>12</sup>     | • Characteristics of the included studies were presented | • Unclear reporting of statistical methods for combining studies.  
   • Literature search did not appear to be comprehensive  
   • No list of excluded studies  
   • No quality assessment of included studies  
   • Conflict of interest was not stated |
| **Randomized Controlled Trials** |           |             |
| Klaus, 2011<sup>13</sup>     | • Appropriate method of randomization described.  
   • Allocation was concealed  
   • All study personal and patients were blinded  
   • Similar loss to follow-up between treatment arms | • Did not present and intention-to-treat analysis |
| Reid, 2009<sup>14</sup>      | • Appropriate method of randomization described.  
   • All study personal and patients were blinded  
   • Similar loss to follow-up between treatment arms | • Unclear if allocation was concealed |
| Mok, 2008<sup>15</sup>       | • Appropriate method of randomization described.  
   • Intention-to-treat analysis | • Unclear if allocation was concealed  
   • Unclear if clinicians and data collectors were blinded. |
<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Abitbol, 2007<sup>16</sup>   | • Appropriate method of randomization described. | • Unclear if allocation was concealed  
• Unclear if data collectors were blinded  
• Unbalanced loss to follow-up |
| Kikuchi, 2007<sup>17</sup>   | • Appropriate method of randomization described.  
• No participants were lost to follow-up | • Unclear if allocation was concealed  
• No blinding in the study (open-label) |
| de Nijs, 2006<sup>18</sup>   | • Appropriate method of randomization described.  
• Allocation was concealed | • Unclear if data collectors were blinded  
• Unclear if an intention-to-treat analysis was used |
| Van Offel, 2001<sup>19</sup> | • Appropriate method of randomization described. | • Unclear if allocation was concealed  
• Loss to follow-up not reported  
• Unclear if an intention-to-treat analysis was used |
## Appendix 5: Main Study Findings and Authors’ Conclusions

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Main Findings</th>
<th>Authors’ Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systematic Reviews</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kanis, 2007</td>
<td><strong>Etidronate</strong></td>
<td>The decrease in risk of non-vertebral fractures was not statistically significant for any intervention. Of the bisphosphonates, only risendronate had a significant effect on vertebral fracture risk.*</td>
</tr>
<tr>
<td></td>
<td>Pooled RR of vertebral fractures from four studies was 0.59 (95% CI: 0.27 to 1.32).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-vertebral fracture risk was not presented separately for prevention studies</td>
<td></td>
</tr>
<tr>
<td>Ibandronate</td>
<td>In one study, the numbers of vertebral and non-vertebral fractures were the same for treatment and control groups.</td>
<td></td>
</tr>
<tr>
<td>Pamidronate</td>
<td>RR of vertebral fracture was 3.62 (95% CI: 0.39 to 33.21) and the RR of non-vertebral fracture was RR 1.16 (95% CI: 0.08 to 17.94) compared to placebo in one study.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RR of vertebral fracture was 0.29 (95% CI: 0.01 to 6.50) compared to calcitonin and calcitriol in one study.</td>
<td></td>
</tr>
<tr>
<td>Risendronate</td>
<td>RR non-vertebral fractures from one study was 0.76 (95% CI: 0.18 to 3.28) with 5mg dose.</td>
<td>Bisphosphonates effectively prevent vertebral bone loss in patients treated with long-term corticosteroids.</td>
</tr>
<tr>
<td></td>
<td>RR non-vertebral fractures from one study was 0.77 (95% CI: 0.18 to 3.32) with 2.5 mg dose.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RR vertebral fractures from one study was 0.64 (95% CI 0.19 to 2.18) with 2.5 mg dose.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RR vertebral fractures from one study was 0.33 (95% CI 0.09 to 1.14) with 5mg dose.</td>
<td></td>
</tr>
<tr>
<td>Blair, 2000</td>
<td><strong>Etidronate</strong></td>
<td>Bisphosphonates effectively prevent vertebral bone loss in patients treated with long-term corticosteroids.</td>
</tr>
<tr>
<td></td>
<td>Across studies, the percent change in lumbar BMD ranged from -0.1 to 1.8 with etidronate and -1.94 to -3.23 with control.</td>
<td>Bisphosphonates effectively prevent vertebral bone loss in patients treated with long-term corticosteroids.</td>
</tr>
<tr>
<td></td>
<td>o Differences were statistically significant in all five studies</td>
<td>Bisphosphonates effectively prevent vertebral bone loss in patients treated with long-term corticosteroids.</td>
</tr>
<tr>
<td></td>
<td>Percent change in trochanter BMD ranged from -1.35 to 1.46 with etidronate and -3.1 to -0.38 with control.</td>
<td>Bisphosphonates effectively prevent vertebral bone loss in patients treated with long-term corticosteroids.</td>
</tr>
<tr>
<td></td>
<td>o Differences were statistically significant in one of three studies</td>
<td>Bisphosphonates effectively prevent vertebral bone loss in patients treated with long-term corticosteroids.</td>
</tr>
<tr>
<td></td>
<td>Percent change in femoral neck BMD ranged from -1.28 to 0.95 with etidronate and -2.59 to -1.5 with control.</td>
<td>Bisphosphonates effectively prevent vertebral bone loss in patients treated with long-term corticosteroids.</td>
</tr>
<tr>
<td></td>
<td>o Differences were not statistically significant all five studies</td>
<td>Bisphosphonates effectively prevent vertebral bone loss in patients treated with long-term corticosteroids.</td>
</tr>
<tr>
<td></td>
<td><strong>Risendronate</strong></td>
<td>Bisphosphonates effectively prevent vertebral bone loss in patients treated with long-term corticosteroids.</td>
</tr>
<tr>
<td></td>
<td>Percent change in lumbar BMD was -0.1 with risendronate and -2.8 with control (p&lt;0.005)</td>
<td>Bisphosphonates effectively prevent vertebral bone loss in patients treated with long-term corticosteroids.</td>
</tr>
<tr>
<td></td>
<td>Percent change in trochanter BMD was -0.2</td>
<td>Bisphosphonates effectively prevent vertebral bone loss in patients treated with long-term corticosteroids.</td>
</tr>
<tr>
<td>First Author, Publication Year</td>
<td>Main Findings</td>
<td>Authors’ Conclusions</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------</td>
<td>----------------------</td>
</tr>
<tr>
<td><strong>Homnik, 2000</strong>¹¹</td>
<td>Etidronate</td>
<td>Bisphosphonates appear to be efficacious at preventing corticosteroid-induced BMD loss in the lumbar spine</td>
</tr>
<tr>
<td></td>
<td>Pooled mean difference in percent change in lumbar BMD after 12 months was 4.06 (95% CI: 3.25 to 4.86)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Pooled mean difference in percent change in lumbar BMD was 3.7% ± 0.6 (p&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Pooled mean difference in percent change in trochanter BMD was 2.8% ± 0.7 (p&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Pooled mean difference in percent change in femoral neck BMD was 1.7% ± 0.7 (p=0.012)</td>
<td></td>
</tr>
<tr>
<td>**Adachi 2000,**¹²</td>
<td>Etidronate - BMD</td>
<td>Etidronate maintained or increased BMD in the lumbar spine, femoral neck, and trochanter and may be effective in preventing fractures.</td>
</tr>
<tr>
<td></td>
<td>• Pooled mean difference in percent change in lumbar BMD was 4.06 (95% CI: 3.25 to 4.86)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• RR 0.77 (95% CI: 0.25 to 2.35)</td>
<td></td>
</tr>
<tr>
<td><strong>Randomized Controlled Trials</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Klaus, 2011</strong>¹³</td>
<td>BMD – Change in Lumbar Spine T-score from baseline</td>
<td>Zoledronate with calcium and vitamin D should be considered whenever treating an acute flare of Crohn’s disease with corticosteroid.</td>
</tr>
<tr>
<td></td>
<td>• Zoledronate: 0.41 ± 0.19 (37.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Placebo: -0.26 ± 0.21(-27.5%); p=0.006</td>
<td></td>
</tr>
<tr>
<td><strong>Reid, 2009</strong>¹⁴</td>
<td>BMD – Percent change from Baseline in Lumbar Spine</td>
<td>One IV dose of zoledronate provides a greater increase in BMD than daily oral risendronate.</td>
</tr>
<tr>
<td></td>
<td>• Intergroup difference in favour of zoledronate: 1.96% (95% CI: 1.04 to 2.88)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Intergroup difference in favour of zoledronate: 1.33% (95% CI: 0.41 to 2.25)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Intergroup difference in favour of zoledronate: 2.27% (95% CI: 1.15 to 3.39)</td>
<td></td>
</tr>
<tr>
<td><strong>Mok, 2008</strong>¹⁵</td>
<td>BMD – Percent change from Baseline in Lumbar Spine</td>
<td>Risendronate is superior to placebo in preventing loss in BMD in the lumbar spine in patients treated with high dose corticosteroids.</td>
</tr>
<tr>
<td></td>
<td>• Intergroup difference in favour of zoledronate: 1.4% (p=0.03)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Intergroup difference in favour of zoledronate: -0.42% (95% CI: -1.17 to 0.34)</td>
<td></td>
</tr>
<tr>
<td>First Author, Publication Year</td>
<td>Main Findings</td>
<td>Authors’ Conclusions</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------</td>
<td>----------------------</td>
</tr>
</tbody>
</table>
| Abitbol, 2007<sup>16</sup>    | BMD - Percent change from baseline in Lumbar Spine  
   Clodronate: -0.2 ± 4.1%  
   Placebo: -2.0 ± 3.2%; p=NR  
BMD - Percent change from baseline in Femoral Neck  
Clodronate: 2.3 ± 14.3%  
Placebo: -1.7 ± 3.7%; p=NR  
Vertebral Fractures  
No new fractures reported in either group | In patients with inflammatory bowel disease, clodronate is effective in preventing bone loss related to corticosteroids. |
| Kikuchi, 2007<sup>17</sup>    | BMD - Percent change from baseline in Lumbar Spine  
Risendronate: 0.96%  
Risendronate and alfacalcidol: 2.0%  
Alfacalcidol: -5.6%; p=NR  
BMD - Percent change from baseline in Femoral Neck  
Intergroup difference in favour of alendronate: 4.0% (95% CI: 2.4 to 5.5)  
Intergroup difference in favour of alendronate: 3.4% (95% CI: 1.3 to 5.5)  
Intergroup difference in favour of alendronate: 3.0% (95% CI: 0.8 to 5.2)  
New Vertebral Deformity  
Alendronate group – 3 patients  
Alfacalcidol group – 13 patients; HR: 0.4 (95% CI: 0.1 to 1.4)  
Nonvertebral Fractures  
Alendronate group – 2 patients  
Alfacalcidol group – 3 patients; HR: 0.7 (95% CI: 0.1 to 4.0)  
| Loss of BMD in the lumbar spine associated with corticosteroid use can be prevented with bisphosphonates, but not alfacalcidol alone. |
| de Nijs, 2006<sup>18</sup>    | BMD - Change from Baseline in the Lumbar Spine  
Pamidronate: 3.8%  
Pamidronate increases BMD despite treatment with corticosteroids. |
| Van Offel, 2001<sup>19</sup>  | BMD - Change from Baseline in the Lumbar Spine  
Pamidronate: 3.8%  
Pamidronate increases BMD despite treatment with corticosteroids. |
<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Main Findings</th>
<th>Authors’ Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo: -2.5%; p=NR BMD described as unchanged in either group for the femoral neck and hand.</td>
<td></td>
</tr>
</tbody>
</table>

BMD=bone mineral density; CI=confidence interval; HR=hazard ratio; NR=not reported; NS=not significance; RR=relative risk; *

* This conclusion was not specific to prevention studies.