Long-term treatment of osteoporosis patients with bisphosphonates

Today, treatment with bisphosphonates is considered the most well-established treatment for osteoporosis patients [1]. And since the number of osteoporosis patients receiving bisphosphonates is increasing, it is even more crucial to provide an overview of the latest knowledge about long-term treatment to assist in improving the basis for providing a safer treatment.

Bisphosphonates - a common treatment regimen in Denmark

When primary preventive treatment with calcium and vitamin D has proved insufficient, bisphosphonates are the most commonly used treatment regimen for osteoporosis in Denmark [1]. Table 1 shows the bisphosphonates that are used in Denmark to treat osteoporosis.

Table 1. Bisphosphonates marketed in Denmark for the treatment of osteoporosis. Bisphosphonates without the indication osteoporosis are not included here. These include Bonefos (clodronate), Pamidronatdinitrium ( pamidronate), Bondronat® (ibandronate) and Zometa® (zoledronate). M: Marketed, D: Deregistered

<table>
<thead>
<tr>
<th>Medicinal product name</th>
<th>Active substance</th>
<th>Strength/dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fosamax® once a week tablet, etc. (M:2001)</td>
<td>Alendronate</td>
<td>70 mg once weekly tablets</td>
</tr>
<tr>
<td>Fosamax® (M:1995)</td>
<td>10 mg once weekly tablets</td>
<td></td>
</tr>
<tr>
<td>Fosavance® (M:2005)</td>
<td>Alendronate/Cholecalciferol Vitamin D3</td>
<td>70mg/70μg once weekly tablets</td>
</tr>
<tr>
<td>Bonviva** (M:2005)</td>
<td>Ibandronate</td>
<td>150 mg once monthly tablets</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Injection 1 mg/ml/ 3 mg i.v. every three months</td>
</tr>
<tr>
<td>Optinate® Septimum etc. (M:2004)</td>
<td>Risedronate</td>
<td>35 mg once weekly tablets</td>
</tr>
<tr>
<td>Aclasta® (M:2007)</td>
<td>Zoledronate</td>
<td>Solution for infusion, 5 mg/ml/ for 15 minutes once a year.</td>
</tr>
</tbody>
</table>

*Didronate®, which contains etidronate (M: 1983 – D: 2010), was not authorised for osteoporosis treatment, but was authorised in 1994 for the treatment of patients with osteopenia and patients at high risk of vertebral compression fractures.

** Bonviva is only authorised for the prevention of vertebral fractures.
According to the Danish Medicines Agency’s Register of Medicinal Product Statistics, 1.5 % of the total Danish population and 5.6 % of women aged over 45 years were treated with bisphosphonates in 2010.

In only six years, the number of users has doubled from approx. 40,000 in 2004 to more than 80,000 in 2010 (see figure 1).

Figure 1: Consumption of bisphosphonates for osteoporosis treatment. Total number of users and new users stated annually. New users are users having redeemed their first prescription for bisphosphonates in the year concerned.

The number of new users is increasing, and in 2010 one fifth of all users were new users. However, the increase in the number of new users is significantly less than the increase in the total number of users, which indicates that a large proportion of patients remain in treatment.

Figure 2: The Kaplan Meier curve of the duration of treatment for patients treated with bisphosphonates from 1 January 1996 to 31 December 2010 (123,698 users in total). Excluded are users who redeemed less than three prescriptions. The duration of treatment is calculated based on average daily doses (DDD), where 1 DDD = 1 day.
When first users have been established in bisphosphonate therapy, they often continue long-term treatment, in some cases even for life (see figure 2). Half of the patients who start bisphosphonate treatment remain in treatment after nearly eight years. The graph in figure 2 does not take into account any breaks in the duration of treatment, and the clinical treatment may therefore be longer than the figure shows.

The probability that the users are still in treatment after five years is 65 %, and it is therefore important to obtain more knowledge about the efficacy and safety of long-term treatment.

In order to focus on the duration of established therapy, users who have redeemed less than three prescriptions are not included in the model. The model can therefore not be used to assess compliance in the beginning of treatment, which, as shown in earlier studies, is often low.

**Limited knowledge about long-term treatment with bisphosphonates**

The clinical studies which formed the basis for authorisation of bisphosphonates have a three to four years' duration, and some of these studies have a follow-up phase of two to three years. This is a relatively long period compared to other studies of medicines. Within a treatment period of up to five years, bisphosphonates treatment for osteoporosis patients is well-documented, but when the treatment period exceeds five years, we lack evidence for the safety and efficacy of bisphosphonates. Only the so-called FLEX study has examined the long-term effect of alendronate treatment, and the study has not provided new knowledge about the safety of long-term treatment with bisphosphonates.
The FLEX study finds a significantly lower risk for clinical spinal fractures but not for morphometric vertebral fractures after 10 years continued treatment compared to treatment ending after five years. There was no effect on non-vertebral fractures. [2].

In a later post hoc analysis of the same study, the patients were grouped according to bone density and history of fractures. In one of the analyses, a reduction in the incidence of non-vertebral fractures was found, limited to women without a history of fractures, but with a femoral neck T-scores of < -2.5 [3].

It is still disputed what these differences mean in practice as evidenced by a recently published article. In the article, the author emphasises that in the FLEX study almost no differences are seen for most fracture types in continued treatment for up to 10 years and concludes that the evidence for further effect of alendronate when given for periods of up to 10 years is very limited and that the study is based on data sets where a sizeable share of patients dropped out of the study population [4].

A study which examined the consumption of risedronate finds no increased benefit of seven years of treatment compared to treatment after three to four years [5].

**Possible long-term adverse reactions - newest knowledge**

**Spontaneous adverse reaction reports - significant in learning more about possible long-term adverse reactions**

The most common adverse reactions seen in clinical trials of bisphosphonates are gastrointestinal effects and influenza-like symptoms. As at 31 July 2011, the Danish Medicines Agency had registered a little over 400 adverse reaction reports for bisphosphonates in the adverse reaction database. The vast majority describe gastrointestinal symptoms and muscle and joint symptoms, which is fully consistent with the results of the studies.

Spontaneous adverse reaction reports from clinical use and from the published literature are essential in monitoring rare adverse reactions and adverse reactions associated with long-term use.

Along with other factors, it was the reported adverse reactions that prompted a further analysis of atypical stress fractures, osteonecrosis of the jaw (ONJ), oesophageal cancer as possible long-term adverse reactions of bisphosphonate therapy. Today, ONJ is a recognised adverse reaction, whereas for oesophageal cancer there is not sufficient evidence. Atypical stress fractures are still being evaluated as a possible long-term adverse reaction.
**Atypical stress fractures**

The evidence for atypical stress fractures as a long-term adverse reaction of bisphosphonate therapy comes from a review of reported adverse reactions as well as newly published studies [6, 15].

Most cases of atypical stress fractures are seen in patients treated with alendronate. In a recently completed European review of reported adverse reactions, the median time from commencement of alendronate treatment to the time of fracture was five years, with symptom onset varying from one to 12 years of treatment. In many of the cases, the patient experienced femoral pain before sustaining a complete femoral fracture. Most fractures were bilateral and were also reported as healing with difficulty. Fractures associated with the use of other bisphosphonates were also reported, but at a much lower frequency.

In Denmark, one case of atypical stress fracture after 10 years' use of alendronate has been reported.

It is a possibility that long-term suppression of bone turnover could result in an underlying pathophysiological mechanism whereby accumulation of micro damage and changes in bone mineralisation may pose a risk of this special type of fractures [7]. All bisphosphonates impact bone turnover, which makes it plausible that atypical fracture is a class effect, which – for reasons of usage and duration of treatment - so far has been seen for alendronate primarily. This is also reflected in the outcome of the recent European assessment, which led to the decision to add warnings to the summaries of product characteristics for all bisphosphonates.

Generally, the risk of atypical fractures is considered to be low, and several studies have shown that the prevention of osteoporosis-induced fractures is significantly higher than the risk for atypical stress fractures [8].

**Osteonecrosis of the jaw (ONJ)**

ONJ is a rare adverse reaction. Studies have shown that the risk of ONJ is much higher in cancer patients treated intravenously (0.8 % – 12 %) compared to oral treatment of osteoporosis patients (0.0004% - 0.06 %) [9]. This difference is, however, not assessed to be due to different indications, but rather differences in potency, cumulative doses and routes of administration between the two patient groups - worth noting in this context is that zoledronate, the most potent bisphosphonate, is now also authorised for once a year intravenous treatment of osteoporosis (see table 1).
The underlying pathophysiological mechanism for ONJ is still unknown, but bisphosphonate-induced impact on the immune system and on local jaw vascularisation [10] as well as actinomyces infection are suspected of being contributory causes [11].

The Danish Medicines Agency has registered 46 cases of ONJ. There has been reported four cases of ONJ following use of alendronate as well as one case of ONJ from the use of Bonviva (ibandronate) for osteoporosis treatment. The remainder are all related to bisphosphonates used in cancer treatment, of which 35 are related to Zometa (zoledronate).

**Oesophageal cancer**

Since it is well-known that bisphosphonates could cause gastrointestinal effects, including gastric ulcers and oesophagitis, oesophageal cancer has long been monitored by national and international authorities as a possible risk of oral treatment with bisphosphonates. Three studies on this possible causal relationship have been published recently [12-14]. However, the results are not clear-cut, and a recent EU review did not find adequate evidence supporting a causal relationship between bisphosphonates and oesophageal cancer.

In Denmark, one case of oesophageal cancer has been reported following treatment with bisphosphonates. The report concerns an osteoporosis patient treated with Bonviva (ibandronate) who, after just one year's treatment, developed metastatic oesophageal cancer.

**Possible measures to increase patient safety**

Investigators and authorities in Denmark and abroad have looked into different measures that could increase the safety for patients treated with bisphosphonates.

For many osteoporosis patients the risk of fractures is so high that continued treatment with bisphosphonates is their most optimal choice. But the weighing of benefits and risks is more complex when it comes to osteoporosis patients for whom the risk of fractures is smaller. Doctors are therefore advised to critically evaluate the treatment for the individual patient after five years [15]. At present, there is no model to determine the absolute risk of fractures involved for patients in long-term treatment with bisphosphonates.

However, there are indications that it is possible to pause treatment with bisphosphonates because studies have shown that bisphosphonates with higher affinity, especially alendronate and zoledronate, bind to the bone and could release the active substance over several years with a beneficial effect [16-18], but it has not been clinically proven what consequences a pause will have for compliant patients who have been treated for several years.
The new NICE guideline from January 2011 calls for more studies in order to define the optimal duration of treatment with bisphosphonates [19], and research into the long-term effect of bisphosphonates on bone turnover has been given special priority by the European Medicines Agency in 2010 [10].

For the most recently approved bisphosphonates, Aclasta® and Bonviva, risk management plans have been established according to which the companies are obliged to continue monitoring patients from the clinical trials.

**Special areas of attention in clinical practice**

Until further clarification has been obtained about the long-term effect of treatment, it is important to stay attentive to symptoms in patients receiving bisphosphonates that could suggest long-term adverse reactions.

- Prolonged femoral pain (going on for weeks or months) could be a symptom of atypical fractures.

- Dental hygiene is particularly important for patients treated with bisphosphonates to avoid invasive dental procedures due to the risk of ONJ. Patients should therefore be advised to have a dental check before they start taking bisphosphonates, so as to go ahead with any impending, major invasive dental procedures before treatment is commenced.

- Symptoms such as oesophagitis, arising after long-term, problem-free treatment, must be examined, and it should be considered to change treatment regimen if oesophageal irritation persists.

In addition, it is important to assess the possibilities for stopping treatment in certain patient groups based on BMD and the patient's other risk factors (low risk of fractures).

Last but not least, adverse reaction reports indisputably play an important role in discovering and monitoring new possible adverse reactions, and it is therefore important to keep reporting any serious adverse reactions observed in clinical practice.
References


