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# The role of *i.v.* ibandronate administration in osteoporosis therapy

## Rola dożylnej postaci ibandronianu w terapii osteoporozy

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**Abstract**

Osteoporosis is a chronic disease of the osseous system characterised by decreased strength of bone tissue, which in turn leads to increased fracture risk. It has been demonstrated that osteoporosis affects more than 30% of women after the menopause (WHO, 1994). However, the disease is also observed in men.

The primary goals of osteoporosis therapy include prevention of low-energy fractures and general improvement of quality of life. Any patient with diagnosed osteoporosis requires, besides prevention, the application of proper treatment.

Of the available therapeutic options, the best are bisphosphonates, medical agents with well identified properties, therapeutic efficacy, and safety which has been confirmed in many clinical studies. Therefore, they are recommended as first line drugs for osteoporosis. The efficacy of oral preparations may be limited, due to low bioavailability, complications and adverse effects from the gastrointestinal tract. So the parenteral administration of bisphosphonates is a valuable alternative. A fine example of such therapy is the intravenous administration of ibandronate. Short injection time periods and the relatively long, three-month intervals between administrations are unquestionable advantages of this therapy mode. In addition, the therapy does not constrain a patient's everyday activity, and simultaneously provides regular contact with doctors and the therapeutic centre. Additionally, a good tolerance of the drug and its high therapeutic efficacy, proven by appreciably reduced fracture risks, significantly improves the quality of life of patients suffering from osteoporosis.

This paper is a thorough review of current knowledge on the efficacy and safety of i.v. ibandronate in osteoporosis therapy, as presented in the latest literature reports. **(Pol J Endocrinol 2011; 62 (1): 51–60)**

***Key words:*** *ibandronate, intravenous, osteoporosis*

**Streszczenie**

Osteoporoza jest przewlekłą chorobą układu kostnego charakteryzującą się obniżeniem wytrzymałości kości, co z kolei prowadzi do zwiększonego ryzyka złamań. Wykazano, że na osteoporozę choruje obecnie powyżej 30% kobiet po menopauzie (Światowa Organizacja Zdrowia, 1994), ale dotyczy ona również mężczyzn.

Celem leczenia osteoporozy jest zapobieganie powstawaniu niskoenergetycznych złamań kości oraz poprawa jakości życia pacjentów. Osoba, u której rozpoznano osteoporozę oprócz prewencji, wymaga również wdrożenia właściwego leczenia.

Spośród dostępnych opcji terapeutycznych kluczową rolę odgrywają bisfosfoniany, leki o najlepiej poznanych właściwościach, których skuteczność terapeutyczna i bezpieczeństwo stosowania potwierdzono w licznych badaniach klinicznych i z tego względu zalecane są jako leki pierwszego rzutu. Skuteczność doustnych preparatów może być ograniczona z uwagi na niską biodostępność oraz powikłania i działania niepożądane ze strony przewodu pokarmowego. Alternatywę stanowi podawanie bisfosfonianów parenteralnie. Forma dożylna ibandronianu stanowi doskonały przykład takiego leczenia. Zaletą podawania dożylnego jest krótki czas iniekcji i dość długa, 3-miesięczna, przerwa pomiędzy podaniami co jednocześnie nie utrudnia chorym codziennej aktywności oraz zapewnia relatywnie częsty kontakt z ośrodkiem leczenia oraz z lekarzem. Dodatkowo dobra tolerancja leku i skuteczność w postaci zmniejszonego ryzyka złamań w znaczny sposób może wpłynąć na jakość życia chorych. Obecny artykuł stanowi aktualny przegląd piśmiennictwa dotyczącego skuteczności i bezpieczeństwa stosowania formy dożylnej ibandronianu w terapii osteoporozy. **(Endokrynol Pol 2011; 62 (1): 51–60)**

***Słowa kluczowe:*** *ibandronian, postać dożylna, osteoporoza*

## Introduction

Osteoporosis is a chronic disease of the osseous system of subclinical course. It has been demonstrated that osteoporosis affects more than 30% of women after the menopause (WHO, 1994) but the disease is also observed in men. According to the World Health Organisation's definition, osteoporosis corresponds to low bone mineral density (BMD), responding in densitometric examination with a T-*score* L –2.5 SD vs. the peak bone mass. At present, low BMD is one of the criteria to start therapy, while fracture risk evaluation is also recommended. Discussions are also being held on the use of calculators for ten-year fracture risk evaluation, taking into account other significant factors beside bone mineral density [1–5].

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The goals of osteoporosis treatment include prevention of low-energy bone fractures and improvement of quality of life. As in any chronic disease, prevention is necessary, with a particular consideration of healthy lifestyle, i.e. balanced diet with proper calcium supplementation, physical activity and the elimination, total or partial of stimulants. A patient in whom osteoporosis has been diagnosed requires an effective therapy to be implemented. Drug selection should take into consideration not only medical contraindications but also individual patient preferences, because osteoporosis therapy is a long-term procedure, often lasting until the end of the patient's life. Bisphosphonates play the key role among the available therapeutic options, as the drugs with the best known properties. With their therapeutic efficacy and safety, which have been confirmed in numerous clinical studies, they are recommended as first-line drugs for osteoporosis treatment [6–13].



## The mechanism of action

Bisphosphonates demonstrate strong antiresorptive effects by inhibiting the activity and inducing apoptosis of osteoclasts and, indirectly, by modulating the activity of osteoblasts [14]. They are used to treat many diseases, including primary osteoporosis and many forms of secondary osteoporosis, hypercalcaemia, which is often a condition concomitant to neoplastic diseases, neoplastic metastases to bones, Paget's disease and bone marrow diseases such as multiple myeloma. Due to the presence of the phosphate group, bisphosphonates bind with hydroxyapatite calcium.

Actually, two distinct molecular mechanisms explain the mode of bisphosphonate activity on osteoclasts. The effect, exerted by the activity of these drugs, depends on the structure and localisation of the lateral chain (Table I) [15]. Bisphosphonates, which do not contain the amine group (tiludronate, etidronate, clodronate) are metabolised by osteoclasts and macrophages to a toxic form of the methylene-containing ATP (adenosine-5′-triphosphate) analogue [16, 17]. Nitrogen-containing bisphosponates (aminobisphosphonates: ibandronate, alendronate, pamidronate, risedronate, zoledronate) block the pathway of mevalonate transformations, limiting in this way prenylation of small GTP-ase proteins, which play an important role in the activity of osteoclasts.

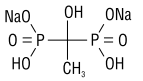
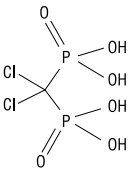
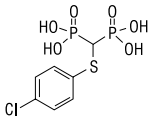
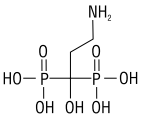
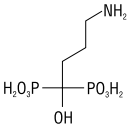
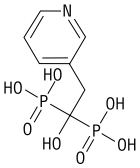
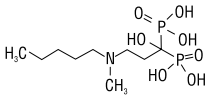
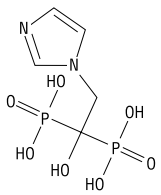
Because of these transformations, the activity of the above-mentioned cells becomes limited, replaced by their enhanced apoptosis. Moreover, ibandronate, which belongs to this particular group, additionally inhibits the process of squalene synthesis. In a culture of mouse osteoblasts and osteocytes, the above-mentioned bisphosphonate suppressed apoptosis induction in those cells [18].

## Ibandronate in oral dosing

Ibandronic acid belongs to bisphosphonates of the third, i.e. the latest generation. It demonstrates a much stronger antiresorptive activity than that of alendronate, another bisphosphonate, and one of which the use is fairly widespread. The efficacy and safety of ibandronate has been confirmed in two large clinical trials: BONE and MOBILE [19, 20]. In the BONE trial (oral iBandronate Osteoporosis vertebral fracture trial in North America and Europe), 2,946 women with osteoporosis were subjected to a three-year observation. All the patients had experienced menopause at least five years previously, their BMD varied from –5.0 to –2.0 SD in the lumbar spine, and each of them presented with at least one vertebral fracture in $Th_4$–$L_4$ section. They received an oral placebo or ibandronate in one of the available forms of administration: 2.5 mg/d or 20 mg every second day (in total: 12 doses for three months). After three years, the incidence of new vertebral fractures significantly decreased in the therapeutic groups, amounting to 4.7% in the group with daily dosage and 4.9% in the group with drug administration every 48 hours, vs. 9.6% in the placebo group. A reduction of the relative risk (RR) for new vertebral fractures was demonstrated by 62% and 50% for daily dosing and for dosing every second day, respectively. Moreover, significantly lower RR of symptomatic vertebral fractures was also obtained for both groups (49% and 48% for ibandronate once daily and once every 48 hours, respectively). The results of a post hoc analysis proved that daily use of the drug reduced the risk of non-vertebral fractures by 69% in a group of patients with increased risks (BMD of the femoral neck — T-*score* ≤ –3.0). Ibandronate was well tolerated during the whole period of the trial [19].

The MOBILE (Monthly Oral iBandronate In Ladies) trial was a randomised, two-year study, double-blinded and comparing the efficacy of oral ibandronate with various dosing modes (2.5 mg/d, 50 mg/month, 100 mg/month or 150 mg/month). The trial was performed in a group of 1,609 women with post-menopausal osteoporosis. After two years of therapy, similar effects were observed in the therapy with ibandronate 2.5 mg once daily and 50 mg, 100 mg, once a month, while significantly better effects regarding increased BMD in the lumbar spine were noted with the dose of 150 mg (increase by 5.0%, 5.3%, 5.6% and 6.6%, respectively). A statistically significant increase of BMD within the total hip, the femoral neck and the trochanter of the femoral bone was noted in all the groups, with the most beneficial effect coming with the dose of 150 mg/month [20]. Considering the scarcity of data on the efficacy of ibandronate in the prophylactics and therapy of os-

**Table I.** *Biochemical structure and division of bisphosphonates according to antiresorptive potential*
**Tabela I.** *Struktura biochemiczna i podział bisfosfonianów według potencjału antyresorpcyjnego*

| Generation | Chemical structure — lateral chain | Biochemical structure | Drug | Antiresorptive potential |
|---|---|---|---|---|
| I | Alkyl |  | Etidronate | 1 |
| | Halide |  | Clodronate | 10 |
| II | Cyclic |  | Tiludronate | 10 |
| | Cyclic |  | Pamidronate | 100 |
| | Amine |  | Alendronate | 100–1000 |
| III | Pyridinyl Cyclic |  | Risedronate | 1000–10 000 |
| | Cyclic |  | Ibandronate | 1000–10 000 |
| | Cyclic |  | Zoledronate | ↑ 10 000 |

teoporosis in men, attention should be paid to recently published data from the randomised STRONG (the STudy Researching Osteoporosis iN Guys) study. That observation comprised 132 men with primarily low BMD and diagnosed hypogonadism. The patients received oral ibandronate, 150 mg/month or a placebo for 12 months. A statistically significant increase of BMD was noted in the lumbar spine (3.5 vs. 0.9%; $p < 0.001$) and in the hip (1.8 vs. –0.3%; $p < 0.001$) in the therapeutic group [21].

Studies of patient preferences provided the following results: BALTO I and II (Bonviva Alendronate Trial

in Osteoporosis) [22], PERSIST (Persistence Study of Ibandronate versus Alendronate) [23], CURRENT [24] and PRIOR [25] revealed that patients preferred ibandronate therapy at 150 mg doses, received once a month rather than more frequently received alendronate. That effect can partially be explained by a better tolerance for the less frequently received drug. Moreover, the annual observation in the MOTION trial demonstrated a comparable therapeutic efficacy of monthly ibandronate and weekly alendronate. BMD increase obtained after 12 months of therapy for ibandronate and alendronate was 5.1% and 5.8%, respectively, in the lumbar spine section and 2.9% and 3.0%, respectively in the hip. Both therapies were well tolerated by the patients [26, 27].

## Ibandronate in intravenous application

### *Preclinical studies*

Due to the potential risk of acute renal failure (ARF), most bisphosphonates are administered in slow-rate intravenous infusions. It has been observed in some studies that, following fast intravenous injection or using big doses, some older bisphosphopnates may induce ARF [28–30]. However, unlike other bisphosphonates, ibandronate can be administered in a quick bolus, without any negative effects on renal functions.

Pfister et al. [31] studied the nephrotoxic properties of intravenously administered ibandronate and zoledronate in rats, using minimal nephrotoxic doses of either compound. The rodents were administered ibandronate (1 mg/kg) or zoledronate (1 and 3 mg/kg), either intermittently, at three-week intervals, or in a single dose for 25 weeks. In the case of ibandronate, the nephrotoxic effects were minimal and independent of the applied administration scheme. On the contrary, renal lesions in the zoledronate-treated rats were distinctive and more intense in the subgroup with the intermittent administration scheme [31]. Ibandronate safety with regards to nephrotoxicity was also evaluated in patients with bone metastases and neoplastic hypercalcaemia in the course of breast carcinoma. Using two-hour infusions of ibandronate in 6 mg doses, a low percentage of acute renal complications was observed [32]. Those data were comparable with placebo results [33––35] and the applied doses were much higher from the therapeutic doses, currently used in osteoporosis therapy. In another clinical project, daily infusions of ibandronate: 4 mg doses in a two-hour infusion, repeated for four subsequent days or 6 mg doses in one-hour infusion, repeated for three subsequent days, to alleviate bone pains in patients with bone metastases, were not associated with any renal lesions [36]. Studies in healthy volunteers and in patients with neoplastic metastases to bones, in the course of breast carcinoma or multiple myeloma, have also confirmed the safety of single, 15-minute infusions of ibandronate in 6 mg doses [37, 38]. In another study, no renal complications were observed after quick injections of ibandronate in 2mg or 3 mg doses in patients with metastases to the bone system [32, 33].

### *Clinical studies of intravenous ibandronate*

Thiébaud et al. [39] were the first to study the efficacy of intravenous ibandronate in the therapy of menopausal osteoporosis. In a planned, randomised, double-blinded trial, 125 women participated (mean age 64 years). The patients received the tested drug in doses of 0.25 mg, 0.5 mg, 1 mg and 2 mg or a placebo every three months. Additionally, each of the participating patients received a calcium supplement. After 12 months, in the groups of patients on ibandronate, an increase of BMD in the lumbar spine was noted by 2.4%, 3.5%, 3.7% and 5.2%, respectively for the increasing doses of the compound. The obtained results were significantly higher vs. those in the control group: 0.5 mg ($p < 0.05$), 1 mg ($p < 0.005$), 2 mg ($p < 0.001$). The study did not show any statistically significant differences among the therapeutic (i.e. drug-receiving) groups. Unlike with the spine, BMD changes in the femoral neck were, in the course of treatment, comparable in all the groups. However, the favourable effects of the increasing doses on the proximal epiphysis of the femoral bone were also successfully demonstrated for its remaining parts. An increase of BMD by 1.8% and 2.9% in the total hip and by 2.7% and 4.2% in the trochanter, was obtained for 1 and 2 mg doses respectively, of the tested drug. The dynamics of bone marker concentrations, observed in the course of therapy, seem to confirm the favourable effects of ibandronate. After the first month of treatment, the concentrations of C-terminal telopeptide of collagen type I (CTX) and of the N-terminal telopeptide of collagen I (NTX) in urine were reduced by 33% (0.25 mg), 44% (0.5 mg), 57% (1 mg) and 66% (2 mg), showing, however, gradual increases as the time of subsequent injection approached. Moreover, the highest (2 mg) dose caused a significant and permanent reduction of the above-mentioned bone markers by 40% ($p < 0,005$). Despite fairly promising results, the study was too short and the groups included only 25 patients each, which is insufficient for proper statistical significance [39].

Taking into account the promising results of a 12-month observation, another project was implemented to provide evidence for the antifracture effects of intravenously administered ibandronate [40]. The study of antifracture efficacy of intravenous ibandronate was a three-year, randomised, double-blind study of 2,862 women

aged 55–76 with post-menopausal osteoporosis, who met the following criteria: 1–4 vertebral fractures in history and a T-*score* from –2.0 to –5.0 SD in, at least, one of their lumbar vertebrae. The participants, beyond a calcium supplement (500 mg/day) and vitamin $D_3$ (400 IU/d) received either a placebo or ibandronate in doses of 0.5 mg or 1 mg every three months. Using both doses of the drug for three years, a statistically insignificant increase of BMD was noted in the lumbar spine by 2.9% and 4.0%, respectively vs. placebo. A similar effect was noted in the hip (Total Hip), i.e. 2.3% and 3.6%. Nor did bone resorption marker concentrations present a positive picture, demonstrating concentration drops by 41.4% and 45%, respectively, measured before subsequent injections. Therefore, the confirmed slight antifracture effect should not be surprising. The incidence of new fractures after three years of therapy was 10.7%, 8.7% and 9.2% for the groups receiving a placebo, 0.5 mg and 1 mg of the drug. The differences were statistically insignificant. While performing a per-protocol analysis, it was possible to obtain a 26% ($p = 0.0549$) fracture risk decrease for 1 mg dose of the drug. Similar data was obtained for non-vertebral fractures and hip fractures, but the statistical power of the study did not allow for a reliable analysis of those end-points [40]. The results of the previously discussed study led to a conclusion that a favourable antifracture effect required a higher dose of the agent. A group of 520 women with osteoporosis after menopause, their ages varying between 55 and 75 years, took part in the two-year Intermittent Regimen intravenous Ibandronate Study (IRIS). The patients received either a placebo or ibandronate in intravenous doses of 1 or 2 mg. After the first year of the study, a statistically significant BMD increase was observed, both in the lumbar spine ([5.0% and 2.8% vs. –0.04%] and in the proximal epiphysis of the femoral bone [2.9% and 2.2% vs. 0.6%]) for both applied doses, i.e. 2 mg and 1 mg of ibandronate) respectively vs. placebo. Bone marker concentration changes: CTX and osteocalcin, remained conformable with BMD changes. The therapy was well tolerated. Similarly small numbers of adverse effects were noted in the ibandronate group and in the placebo group and, most importantly, no renal toxicity was induced by the drug in the applied doses. The study duration was planned for two years but, due to the unfavourable results of the three-year observation of antifracture efficacy and to the earlier proven assumptions, the study programme was finished after one year of observation [41].

In the meantime, several other studies were undertaken into the efficacy and safety of intravenous ibandronate. Stakkestad et al. [42] evaluated the efficacy of the therapy in a group of 629 women at a mean age of 54.75 and a maximum 10 years after menopause, in whom osteoporosis had earlier been excluded. A randomised study with placebo and double-blinded, was, as in the IRIS Project, planned for two years. The applied therapy was to have prevented osteoporosis. The women received the drug in 0.5 mg, 1 mg and 2 mg doses every three months. After the first year of therapy, in both studied areas, i.e. the lumbar spine and the hip, a significant BMD increase was found for all the drug doses, with a clear dose-dependent effect. Neither study was continued, due to the already published data from the above-mentioned project of Recker et al. [40] about the lack of therapeutic efficacy of ibandronate in too small a dose: 0.5 mg and 1 mg.

Ringe's team [43] evaluated, in a three-year open study, the therapeutic effects of intravenous ibandronate in patients with steroid-induced osteoporosis. There were 115 participants, who received at least 7.5 mg of prednisone per day for the last two years. The patients, receiving calcium supplementation (500 mg/ /day), were assigned to two groups, one of which was administered alphacalcidiol in a dose of 1 mcg/d or ibandronate in a dose of 2 mg every three months. In patients treated with bisphosphonate, a statistically significant BMD increase was demonstrated, amounting to 13.3% in the spine and 5.2% in the femoral neck vs. 2.6% and 1.9% in the group on an alternative therapy. Despite the fact that the primary end-point of the project was not antifracture effect evaluation, an evidently lower prevalence of vertebral fractures was noted in the ibandronate group vs. alphacalcidiol (8.6% vs. 22.8%).

Moreover, the study in question for the first time proved the efficacy of intravenous bisphosphonates in fracture prevention for patients with steroid-induced osteoporosis. The patients who received ibandronate less frequently reported back pains with a significantly lower height reduction [43]. Other, smaller clinical studies are also worth mentioning, the primary end-points of which were the concentrations of bone markers. Christiansen et al. [44] applied ibandronate in 73 women after menopause and without diagnosed osteoporosis. The patients received either a placebo or the drug in a dose of 1 mg or 2 mg, twice, with a 84-day interval. Serum CTX and osteocalcin concentrations were measured at 19 time points. Following the drug administration, CTX concentration decreased to obtain the lowest level on the seventh day after administration, while, after approximately two weeks from injection, its gradual increase was observed. Immediately before a subsequent drug administration, its concentration was about 16% and 20% lower for a 1 mg and a 2 mg dose, respectively vs. that before therapy. Osteocalcin values in the therapy groups were characterised by a slow decrease, where the lowest concentration (–35%) was observed five months after the study onset. The authors

of the project highlight the relatively short period of resorption suppression (CTX) vs. bone formation (osteocalcin), as the factor at the root of the failure of the three-year antifracture project by Recker's team [40], which may raise certain doubts in the light of later data [44].

The Study of Different Regimens of Intravenous Administration of Bonviva (Ibandronate) in Women With Post-Menopausal Osteoporosis (DIVA) is by far the most important project looking at the registration of intravenous ibandronate. That randomised, double-blinded study was to demonstrate a similar efficacy (non-inferiority) of intravenous ibandronate vs. daily oral form.

A group of 1,395 women, aged 55–80, were qualified to the study. All the patients had experienced menopause at least five years previously and had osteoporosis, diagnosed from a T-*score* parameter in the lumbar spine, below –2.5 SD but not below –5.0 SD. The patients were divided into three groups, receiving oral ibandronate in a dose of 2.5 mg/day and intravenous ibandronate in doses of 2 mg or 3 mg every two or three months, respectively. All the participants were provided with oral calcium (500 mg/d) and vitamin $D_3$ (400 IU/d) supplementation. A two-year follow-up demonstrated intravenous ibandronate to have been not only non-inferior but to have an even higher efficacy in the therapy of osteoporosis. Bone density in the lumbar spine increased by 6.4%, 6.3% and 4.8% in the groups treated with intravenous 3 mg and 2 mg doses and with 2.5 mg/d dose, respectively, where the intravenous therapeutic effect attained the level of significance ($p < 0.001$). Analogous results were obtained, comparing BMD values in the hip and in the femoral bone trochanter ($p < 0.001$).

However, no significant BMD differences were found in the femoral neck region. The efficacy of intravenous doses was similar and the observed differences insignificant. A similar, statistically significant, fall of CTX, from 53.4% to 59.9%, was observed in all the therapeutic groups [45]. In an observation of a subgroup of 109 women, bone biopsy was performed for histomorphometric analysis. Following the results from 89 studied samples and of their comparison with control material, no damage in bone microarchitecture nor impaired bone mineralisation/formation was observed. The collected material demonstrated only features of certain remodelling suppression in results of the therapy [46]. The DIVA study was initially not designed to evaluate differences of antifracture efficacy in both therapy forms. Despite the difference not being statistically significant, observed in the incidence rates of all fractures after two years of the study, a post hoc analysis of the study, performed by Sambrook's et al. [47], demonstrated a significant, 43% reduction of nonvertebral fracture risk ($p < 0.05$) in the group on intravenous bisphosphonate vs. the patients on oral therapy [47]. A metaanalysis of the results, obtained in phase III clinical studies of ibandronate efficacy and safety (BONE, MOBILE, the study of antifracture efficacy of intravenous ibandronate [40], DIVA), presented with antifracture efficacy of both the oral form, in a dose of 150 mg/ /month, and the intravenous form (2 mg every two months and 3 mg every three months). The participants in the studies, using the above-mentioned forms of the drug, demonstrated an almost 30% reduction of the non-vertebral fracture risk and of all symptomatic fracture risks after two years [48]. Because most studies into the efficacy of ibandronate, especially of its intravenous form, have been performed on female populations, the project by Lama et al. deserves special attention [49]. Fourteen men were submitted to a two-year open treatment with intravenous ibandronate in 2 mg doses, administered every three months. After the observation, an increase of BMD was demonstrated in all the studied areas: in the lumbar spine by 6.7% ($p < 0.001$), in the trochanter by 3.2% (NS) and in the femoral neck by 1.4% (NS). The concentrations of bone turnover markers, i.e. CTX and osteocalcin, were reduced by 30–45% and 30%, respectively. The obtained data, however promising, are unsatisfactory in terms of evaluating the efficacy of anti-osteoporotic therapy with intravenous ibandronate in men. It is necessary to design for that purpose a randomised, double-blind study [49]. Attempts have also been undertaken to apply intravenous ibandronate in patients after transplantations. Kaemmerer et al. [50] administered ibandronate in a 2 mg dose every three months for 12 months to 34 patients after liver transplantation. In the therapeutic group, a significantly lower incidence of new fractures and no BMD decreases were demonstrated vs. the control [50].

Another team [51] obtained a favourable effect on BMD loss prevention and decreased fracture incidence, administering the above-mentioned bisphosphonate in the same dose to patients after heart transplantation. After 12 months of the therapy, the incidence of new vertebral fractures in the therapeutic group was 13% vs. 53% in the control group, a difference that was statistically significant [51].

## Safety and tolerance

Ibandronate, administered intravenously in three-month intervals, is, in general, well tolerated by patients. In a three-year study of the antifracture efficacy of the medical agent [40], patients reported adverse events (AE), mostly mild and moderate ones, with a comparable incidence rate in all the studied groups. A slightly higher reportability, i.e. 3 1% in the therapeutic groups,

was accounted to: muscular pains, sinusitis, asthenia, limb pains and adverse reactions to injections. A total of 253 out of 2,862 participants discontinued their treatment because of AE: in the group using 1 mg of the drug 105 participants, , in the group receiving 0.5 mg of ibandronate 77 participants and in the group receiving a placebo 71 participants. The incidence of therapy-related adverse effects was higher in the patients on therapy, amounting to 17% and 15% for 1 mg and 0.5 mg of ibandronate, respectively vs. the patients in the placebo group, 10%. In the great majority, adverse effects included muscular pains and reactions to injections. In as many as 25% of the participants, serious adverse events (SAE) occurred, but their incidence rate was similar in all the studied groups: 23.2% (1 mg), 25.2% (0.5 mg) and 26.7% (placebo). Among the above-mentioned severe adverse events, only five patients (three in the placebo group) experienced SAE, potentially drug-related: stroke (the 1 mg group), cataract (the 0.5 mg group), gastro-intestinal disorders, skin lesions and hypertension (the placebo group). Twenty-nine (1%) patients died during the study but none of the deaths was related to the therapy [40].

In the IRIS study [41], in which slightly higher ibandronate doses were used, a fairly high, but similar in all the groups, incidence of adverse events was observed. In total, 70%, 75% and 71% of AE were recorded for patients, using the drug in 2 mg and 1 mg intravenous doses and receiving the placebo, respectively. The most frequently reported ailments included: back pains and arthralgias, infections of the upper respiratory tract, pseudoinfluenzal symptoms and headaches. An elevated incidence of arthralgias and fever was found in patients on active treatment. In turn, drug-related AEs were observed in 19% (the 2 mg intravenous group), 20% (the 1 mg intravenous group) and 14% (the placebo group).

The differences in the incidence of treatment-related adverse events among the groups were statistically insignificant, although some positive trend was maintained, taking into account the incidence of limb pains, myalgias and arthralgias in patients on intravenous therapy vs. placebo. The above-mentioned symptoms were predominantly short in duration, being most probably associated with the acute phase reaction, which had been observed earlier, when larger intravenous doses of aminobisphosphonates were used.

It is even more important that the majority of such reactions occurred in the study participants only once, following the first drug administration, where the intensity of ailments was mild or moderate, regressing within a maximum of seven days from injection. No drug-related SAE was noted in the study by Adami et al. [41]. Analysing the results of biochemical measurements, no toxicity features were identified with regards to the administered drug, including renal dysfunction. In turn, a refusal to continue the therapy as the result of adverse episodes was more frequently observed in the therapeutic patients: 6%, 3% and 2% of the participants gave up further treatment in the groups using the drug in the doses of 2 mg and 1 mg and placebo, respectively.

During the two-year DIVA study [45], a comparable incidence of treatment-related adverse episodes was observed, as well as of such episodes which caused therapy withdrawal in all the studied groups. The most frequent treatment-related side effects, as found in previous studies, were back pains and arthralgias. Nasopharyngitis was an adverse effect relatively frequently reported by the patients.

No episode of osteonecrosis of the jaw was noted in any of the groups over the course of a two-year observation. This particular adverse event may become a significant problem in the treatment with intravenous bisphosphonates, although it much more frequently concerns patients with metastases into bones or neoplastic hypercalcaemia in the course of breast cancer or multiple myeloma [52, 53]. In the retrospective analysis by Abu-ID et al. [52], only seven cases of jaw osteonecrosis were found in patients on chronic therapy with oral or intravenous ibandronate [52]. An equally low rate of necrosis after ibandronate was demonstrated in another study [53]. Only two cases of this complication after ibandronate were described unitil 2006, and one of these two patients had also been using zoledronate in a chronic therapy mode [53].

Taking into account the obtained data, we assume that the risk of occurrence of this dangerous complication in patients treated with ibandronate to be very small. Prior to application of the therapy, patients are recommended to check their oral caviy and major dental procedures are avoided, if not urgent. In the DIVA study [45], the incidence of severe adverse events was similar in all the studied groups, amounting to: 14.4%; 16.3% and 13.2% for a 3 mg dose every three months, 2 mg dose every two months and oral dose of 2.5 mg/ /day. A total of 11 SAEs was recorded, of which nine resulted in patient death. A similar percentage of participants in the groups gave up further treatment (17–21%), also because of AEs (9.8–11.7%). Similarly as in the IRIS study (with placebo control), pseudoinfluenzal symptoms occurred more frequently in the patients who were using the drug intravenously. However, they were more frequently reported in the group with the dose of 2 mg every two months (15.6%) than 3 mg every three months (10%) and with the oral dose of 2.5 mg/day (4.3%). The intensity of the above-mentioned symptoms was slight or medium and they usually disappeared after seven days from injection. No case of acute renal

failure was noted in the course of the study and the incidence rates of renal parameters lowering were comparable (21–23% of the participants) [45]. Reports have appeared in recent years about an increased risk of atrial fibrillation in patients on chronic bisphosphonate therapy. The results of the very few studies dealing with the complication have not been entirely clear [54, 55]. An analysis of data from four clinical studies (BONE, The study of antifracture efficacy of intravenous ibandronate [41], MOBILE, and DIVA), found a similarly low incidence, i.e. < 1%, of atrial fibrillation, both as adverse events and serious adverse events in patients using ibandronate and a placebo [56].

Derman et al. [57] examined the effect of switching from oral alendronate once a week to ibandronate administered oraly once a month or inravenously every 3 months on the incidence of gastrointestinal adverse events. In 70 % of patients who experienced gastrointestinal disorders during alendronate therapy, a reduction in the frequency and severity of those symptoms were observed after introducing either intravenous or oral ibandronate. After 10 months of treatment with ibandronate, 90% of patients reported a reduction in gastrointestinal symptoms.



## Summary

Oral bisphosphonates have gained an established position in the therapy of osteoporosis. Their efficacy and safety of use have been supported by the results of numerous clinical studies and by practical observations of their many-year applications in patients all over the world [1–8]. However, the period of their use is rather limited due to low bioavailability, complications and adverse symptoms from the gastro-intestinal tract [58––62]. The oral use of bisphosphonates requires strict compliance with recommendations, including fasting after tablet intake and keeping the body in an erect position for longer time periods, which can be associated with some discomfort. All these inconveniences, the patient's general state and her/his individual preferences may impede therapy acceptance by the patient, and this usually compromises the patient's compliance and clinical efficacy in everyday realities of life [63, 64]. The elongation of the time interval between doses to one week (alendronate) met patient expectations only in part; further progress towards optimisation of osteoporosis therapy was the introduction of oral ibandronate protocol with monthly dosing.

Patients with osteoporosis or osteopenia were qualified to the PRIOR study, all of them having previously discontinued their therapy with another oral bisphosphonate. The participants were offered a choice between two forms of therapy: intravenous Bonviva, administered every three months, or the oral form of the drug, received once a month. They could also switch (once) from the first selected drug to another one in the course of study. As many as 82.9% of the participants who decided on the intravenous form, remained with the primary option of therapy, while 69.7% of the patients remained with the primariliy selected oral therapy [25].

The intravenous administration of the drug eliminates the risk of gastro-intestinal adverse effects and increases patient's compliance, most probably for the relatively rare drug applications with the relatively frequent contacts with the drug applying centre. Additionally, taking into account its outstanding bioavailability and high antifracture efficacy, it can indeed be recommended for patients with increased fracture risks. Intravenous ibandronate is an excellent example of such therapy [25]. The drug is administered every three months, which compels a patient's regular attendance at the medical centre and enables frequent contacts with the doctor, whose role is to motivate the patients to continue the therapy, unless adverse symptoms occur, which would require therapy changes. The visit after the first drug administration is very important for the frequently observed pseudoinfluenzal symptoms. The patient should be informed of the slight risk of their recurrence during subsequent drug applications. Both the oral and the intravenous form of ibandronate present with proven antifracture effectiveness and, because of the less frequent administration, they do not impose any necessity to change lifestyle on the treated patient. Results of the previously discussed clinical studies BALTO I and II, CURRENT, PERSIST and PRIOR, unequivocally indicate that patients more frequently choose oral ibandronate, administered once a month, rather than drugs of the same group administered every day or once a week.

Both forms of ibandronate, i.e. oral and intravenous, are good alternatives in the treatment of osteoporosis, especially for those patients who either do not want or cannot receive other bisphosphonates. The advantage of intravenous administration is its outstanding bioavailability, the short time of injection and the fairly long, three-month interval between administrations.

This does not impede a patient's everyday activity, but also ensures relatively frequent contact with the therapeutic centre and the doctor. Additionally, the confirmed good tolerance of the drug and its effectiveness, manifested by reduced fracture risks, may considerably improve the quality of life of treated patients, something which is a key element in the therapy of osteoporosis.

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