Neridronate therapy in the management of fracture risk

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Summary

Neridronate is a nitrogen-containing bisphosphonate and in Italy it is licensed for the treatment of Osteogenesis Imperfecta (OI), Paget’s disease of bone and type I Complex Regional Pain Syndrome. Differently from other bisphosphonates, neridronate can be administered both intravenously and intramuscularly. The latter regimen is noteworthy, especially because it does not require hospitalization and it is therefore suitable for homecare. Furthermore, both the intravenous and intramuscular regimens can prevent the possible side effects associated with the oral route. In this review we will discuss the data on the efficacy of neridronate for different conditions, from OI to post-menopausal osteoporosis, both in terms of bone mineral density changes and of anti-fracture benefit.

KEY WORDS: neridronate; osteogenesis imperfecta; complex regional pain syndrome; bisphosphonates.

Chemical features

Neridronate is a nitrogen-containing bisphosphonate (1) and in Italy it is licensed for the treatment of Osteogenesis Imperfecta (OI), Paget’s disease of bone and type I Complex Regional Pain Syndrome (CRPS-I).

The negative charge of the phosphate group, which constitutes the structural backbone of bisphosphonates, ensures their high affinity for the positively charged calcium ions of the mineralized bone matrix. On the other hand, the two side chains (which bear the carbon atom) are the determinants of the biological activity of the specific molecule and also categorize it according to two different classes (1). The first class is represented by amino-bisphosphonates such as neridronate, pamidronate, alendronate, ibandronate, etc. The second one is represented by non-amo-no-bisphosphonates, as clodronate, etidronate, and tiludronate (1). As known, amino-bisphosphonates are characterized by a higher potency and act by inhibiting the farnesyl pyrophosphate synthase (1, 2). This enzyme plays a key role in the mevalonate pathway and it is necessary for the prenylation of proteins, a fundamental process for the intracellular signaling and regulation of the osteoclast function (2).

Neridronate is structurally similar to alendronate and pamidronate and differs from them only in the number of the methyl groups of the side chain: five for neridronate, three for alendronate, and two for pamidronate (3). Differently from other bisphosphonates, neridronate can be administered both intravenously and intramuscularly. The latter regimen is noteworthy, especially because it does not require hospitalization and it is therefore suitable for homecare. Furthermore, both the intravenous and intramuscular regimens can prevent the possible side effects associated with the oral route. Indeed, although oral bisphosphonates are the treatment of choice for a variety of bone diseases, they have a low oral absorption rate (their oral bioavailability is lower than 1%) (4) and therefore need to be taken while fasting and the intake of food or other drugs needs to be postponed as well. Oral bisphosphonates are also associated with upper gastrointestinal tract adverse events in about 25% of the patients (5) and for this reason their ingestion requires an adequate amount of water and must be taken with an upright posture. All the possible complications associated with the oral administration can contribute to explain their limitations in terms of compliance and adherence to the treatment, thus emphasizing the need for parenteral formulations.

Clinical development

Over the years, neridronate has proven to be effective as an off-label treatment for many clinical bone-related pathologies (6). In Italy it is licensed for the treatment of Paget’s disease of bone, OI (to date it is the only drug registered for this indication) and CRPS-I, on the basis of the results of relevant clinical trials (7-10).

Recently, the results of a long-term neridronate treatment (3 years) in adult (11) and pediatric patients (12) affected by OI have been published. These two studies evaluated the safety and the efficacy of this treatment and reported not only the effects on bone mineral density (BMD), but also on fracture risk, therefore providing new important data regarding the usefulness of this drug in OI. It is now known that, in the setting of OI, the increase of bone turnover is a hallmark of the disease (13), and this notion provides a strong rational for an antiresorptive therapy. Bisphosphonates are commonly prescribed to these patients, and they...
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have been shown to increase BMD in both children and adults (14). However, it is not yet completely proved whether bisphosphonates are able to consistently decrease the fracture risk. Indeed, multiple studies reported this data independently and no study ever observed an increased fracture rate associated with the treatment (14).

Idolazzi et al. (12) reported the data of 55 young OI patients (mean age 12.6 ± 3.9 years) treated every 3 months with i.v. neridronate at a dose of 2 mg/kg (up to a maximum dose of 100 mg) for 3 years. BMD, bone mineral content and the projected area (evaluated by DXA every 6 months) showed a clinically significant (p < 0.001) increase from baseline to all subsequent time points both at the lumbar spine and hip. The mean increase from baseline in lumbar spine BMD after 3 years was over 50%, with a mean improvement of the lumbar spine T-score of 1.3 standard deviations (SD).

However, the main strength of this study regards the effect of the treatment on fracture risk. As known, OI patients have an increased fracture rate throughout their life (15). During the 3 years of neridronate treatment the percentage of patients with new fractures was almost half that of the 3 years preceding the start of the treatment itself (43/55 vs 24/55 respectively). Therefore, 37% of the patients who had experienced at least one fracture in the 3 years before the study did not have any new fracture during the treatment with neridronate (p < 0.001 in the distribution of patients with or without fractures).

The study of Viapiana et al. (11) involved 114 adult OI patients (mean age 40.0 ± 12.45 years) treated every 3 months with i.v. neridronate at a dose of 2 mg/kg (up to a maximum of 100 mg) for 3 years. The mean lumbar spine and total hip BMD significantly increased from baseline to every time point (p < 0.001). As expected, the extent of the improvement was lower than that previously reported in children and adolescents. In this adult population, a significant increase from baseline of ultradistal radius BMD was also reported, but only from the 18th month on. The number of patients suffering from clinical fractures appeared to be unchanged during the 3 years of treatment when compared to the 3 years before (p = 0.19). However, we should consider that in OI patients the fracture risk appears to be very high during their youth and adolescence and in the elderly, while during adulthood it is only mildly increased, achieving similar values to the healthy population (15). In our opinion, this is the main reason why in adults with OI it is somewhat difficult to demonstrate the anti-fracture effect of any therapy. Furthermore, in that study, most of the patients (61.5%) did not suffer from any new fracture when the 3 years of treatment were considered together with the 3 years before. For this very reason, not only the incidence of fractures as expressed by patients who incurred in new events should be analyzed, but also the crude mean amount of all new fractures. From this perspective, the incidence of fractures expressed as mean of new fractures observed in the 3 years of treatment was significantly lower (about 50%) than that observed in the 3 years preceding the start of the treatment. In our opinion, these data strongly support the efficacy neridronate on fracture risk also in the adult patients.

Over the years neridronate has been used, and still is, as a possible off-label treatment for many bone-related conditions (6) and in particular for osteoporosis. Two pilot randomized-controlled trials evaluated the effectiveness of neridronate on BMD in postmenopausal women with osteoporosis. In the first study, 78 women were treated with i.v. neridronate 50 mg every 2 months, over 2 years (16). In the neridronate group BMD rose progressively at the spine up to 7.4 ± 6.1% and at the femoral neck up to 5.8 ± 8.2% at the end of the second year. These positive effects on BMD appear to be similar to the ones obtained in a second pilot study, in which 40 elderly women were treated with monthly intramuscular injections of neridronate 25 mg (17).

Neridronate has also been tested for the prevention of glucocorticoid-induced osteoporosis (18) and in patients affected by beta-thalassemia (19) with positive results on BMD and on pain.

The results of all these studies on osteoporosis indicate that a dose of 25 mg neridronate monthly (administered intramuscularly or intravenously) is arguably the dose providing the maximum effects in this condition. The magnitude of the changes in terms of BMD (Figure 1) seems to be somewhat similar (if not even superior) to those reported after 1 year of treatment with other anti-resorptive drugs currently licensed for the treatment of osteoporosis. Figure 1 reports the data collected from non head-to-head studies, but they support the hypothesis that neridronate 25 mg/monthly might nevertheless be one of the most powerful bisphosphonates in osteoporosis, at least in terms of BMD changes. Unfortunately, the data regarding the effects on fracture risk are still lacking. However, if we consider that there are data from the 2018 ASBMR annual meeting (20) supporting the use of the surrogate effects on BMD as efficacy criteria for the development of new therapies for osteoporosis, new possible opportunities may arise also for neridronate, such as the promotion of a proper clinical bridging trial.

Conclusions

Neridronate is a nitrogen-containing bisphosphonate developed in Italy for the management of several bone diseases. This drug is currently licensed for the treatment of Paget’s disease of bone, OI and CRPS-I. Recent results confirmed the anti-fracture effects in patients of any age affected by OI. However, neridronate, being it suitable to both the intravenous and intramuscular route, could represent a possible alternative to other therapies also in osteoporosis. This possibility appears to be of interest especially in patients with gastric or esophageal disease or in those intolerant to oral bisphosphonates, especially when hospitalization is difficult, and the subject is suitable for homecare.

Disclosures

Angelo Fassio reports personal fees from: Abiogen Pharma and Novartis. Elisabetta Vantaggiato has nothing to disclose. Davide Gatti reports personal fees from: Abiogen Pharma, Amgen, Janssen-Cilag, Mundipharma, Pfeizer.
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