Anti-osteoporotic treatments in neurological diseases

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Summary

The constant ageing of the population has resulted in an increase in chronic conditions such as osteoporosis and neurodegenerative diseases as well as in patient comorbidity. Prolonged immobility, the use of osteopoenia-inducing drugs and an increased risk of falls in patients with neurological diseases have led to an increase in the incidence of fragility fractures, especially of the femur, in these patients. The consequences of these events are often dramatic, being associated with increased mortality, disability and worsening of cognitive and relational functions.
Potent drugs are currently available that can reduce fracture risk by up to 50% with long-term safety and tolerability. Bisphosphonates are the agents most extensively used to prevent fragility fractures. Risedronate has been demonstrated to reduce fracture risk, also in patients with neurological conditions. Considering that osteoporosis requires chronic treatment, patient compliance is extremely important to obtain treatment efficacy.

KEY WORDS: bisphosphonates, fall risk, fragility fractures, immobility, osteoporosis.

Introduction

Osteoporosis is a chronic disease affecting the skeleton that leads to bone loss, bone architecture disruption and reduced bone strength. A person with osteoporosis has increased bone fragility and is more predisposed to fractures.
Primary osteoporosis develops after the menopause (postmenopausal osteoporosis) or in old age (senile osteoporosis) (1). The risk of osteoporosis is increased in elderly people and especially in women, because the menopause and ageing cause faster bone degeneration. However, the condition can also affect relatively young men and women, such as patients taking osteopoenia-inducing drugs [glucocorticoids, thyroid hormones (thyroxin), chemotherapy agents, heparin, anticonvulsants] or those affected by diseases that can cause secondary osteoporosis (e.g. endocrine, blood, renal and gastrointestinal tract diseases, chronic respiratory conditions). Prolonged immobility can also cause osteoporosis (2).
Densitometric diagnosis of osteoporosis is based on the measurement of bone mineral density (BMD) by dual-energy x-ray absorptiometry (DXA). The measured value (T score) is compared with the average density of healthy adult subjects of the same sex (bone density peak). The World Health Organisation has defined guidelines for the diagnosis of osteoporosis based on BMD: normal T score: from +2.5 to -1 SD; osteopoenia T score: from -1 to -2.5 SD; osteoporosis T-score: below -2.5 SD; established osteoporosis: T score below -2.5 SD with one or more fragility fractures (3).
Differential diagnosis, essential in order to establish whether osteoporosis is primary or secondary, must be combined with a comprehensive clinical evaluation of the patient to assess fracture risk based on bone loss severity (given that bone structure accounts for 50% of bone strength). This evaluation will also take into account the presence of risk factors, such as previous fractures, that can increase the likelihood of new fractures (4). Some risk factors can be reduced or eliminated by lifestyle changes, for example, by increasing physical exercise and smoking less, or giving up smoking, or through dietary calcium and vitamin D supplementation (4).
Osteoporosis may have dramatic consequences and, because of its repercussions, is considered a social disease; it is also seen as an under-diagnosed and “silent” condition.
It has been estimated that in Europe 30% of postmenopausal women (5) have osteoporosis. Osteoporosis rates in Italy were estimated in the ESOPO trial (6): approximately 4,000,000 women in Italy are affected by osteoporosis and are at increased risk of hip fracture, with a prevalence of more than 40% in women over sixty.
The most severe complication of osteoporosis is fracture. It has been estimated that in the year 2000, 9 million fragility fractures were recorded all over the world, 1.6 million of which were hip fractures (7). Hip fracture is a very severe condition and can lead to permanent disability in around 50% of elderly people affected. It is indeed a well-established life-threatening event especially in the elderly population. In Western countries, annual mortality rates for hip fractures are now higher than those recorded for gastrointestinal tract and pancreas cancer. It has been estimated that the lifetime risk of hip fracture is, in women, higher than the overall risk of developing breast, endometrial and ovarian cancer, and in men, higher than the risk of developing prostate cancer. Elderly patients with hip fracture are at increased risk of disability, a situation that results in increased health care costs to society. Hip fractures are causing a growth in health care spending in all Western countries. As regards the Italian National Health Service, a recent report showed that in 2002, costs totalling over 1 billion euros were generated by 800,000 hip fractures (8). Other fragility fractures include osteporotic vertebral deformi-

ties, which often occur without the patient experiencing any painful symptoms. Moreover, postmenopausal women with previous vertebral fracture (with and without symptoms) have an increased risk of developing fractures in other sites, including the hip. A careful patient history is essential to assess the severity of osteoporosis and to select the best treatment.

Fragility fractures in patients with neurological diseases

Although no prospective controlled trials have been conducted to establish a correlation between neurological diseases and increased risk of fragility fractures, there exists evidence showing that neurological patients have a higher risk of developing fragility fractures, especially non-vertebral and hip fractures.

Prolonged immobility is an important factor in the state of many patients with neurological conditions (for example, in patients with stroke-induced hemiplegia). Lack of mechanical stress and physical exercise is known to result in rapid and severe trabecular bone loss, with increased early bone resorption and reduced new bone formation. This process, in turn, results in more bone fragility and increased fracture risk. Moreover, immobilised patients are at greater risk of developing vitamin D deficiency due to reduced sunlight exposure and malnutrition. Vitamin D deficiency is known to affect bone metabolism and cause compensatory hyperparathyroidism leading to bone loss and a negative impact on the patient's muscular activity. All this may increase the risk of falls and consequent fractures, especially of the hip, in patients with bone fragility (9).

A longitudinal study of over 4,000 patients demonstrated that the risk of hip fracture in stroke survivors is two- to four-fold greater than that of patients with no previous stroke episodes (10). This finding was confirmed by a study carried out on over 200,000 hospitalised stroke patients, who were found to have a four-fold increased risk of hip fracture during the first year after hospitalisation (11).

A retrospective study showed that over 16% of patients with hip fractures had a previous stroke event (12). Although a number of publications confirm the increased fracture risk in these patients, a report of a 25-year study (13) showed no difference in cumulative fracture risk between stroke patients and controls. However, the patients in this study had not been selected on the basis of the presence of hemiparesis or hemiplegia and few data were provided on stroke severity and increased risk of falls and fractures.

Increased risk of falls and bone fragility are important considerations in stroke patients. Some studies report that 70% of stroke patients experience a fall after hospital discharge (14,15), and most falls in these patients affect the hemiplegic side of the body (16). Fortunately, not all falls cause fractures (15), but they may nevertheless have emotional consequences: 89% of patients who have suffered a fall tend to develop an increased fear of falling (16) and this may lead to reduced socialisation, depression (15) and consequently reduced mobility.

For stroke patients, immobilisation is an additional fracture risk factor associated with reduction in BMD, especially in the hemiplegic side of the body. A study conducted during the rehabilitation of stroke patients reported a 12% reduction in BMD in the paretic side versus a 3.5% reduction in the non-paretic side (17).

Another study on 83 hospitalised stroke patients reported a 40% incidence of osteoporosis (18), even though the authors could not exclude the possibility that osteoporosis had been present well before the stroke event.

An increased risk of falls is also observed in patients treated with drugs that affect attention, including narcotics, analgesics, sedatives, hypnotic agents and antidepressants, as well as in patients with motor impairment (Parkinson's disease) and those with stroke-related reduction of visual function (19). Dementia patients too, for example those with Alzheimer's disease, are at higher risk of fragility fractures probably due immobility-related falls. Weller and Schatzker recently reported that Alzheimer's disease may be an independent risk factor for hip fracture. Further studies are needed to understand these results and provide an in-depth evaluation of the genetic features of these patients (20).

In patients with neurological diseases, the use of drugs that can cause osteoporosis is an additional risk factor leading to increased bone resorption and fragility. The risk of developing fragility fractures is increased in epilepsy, in which chronic use of anticonvulsants, particularly phenytoin and barbiturates, leads to a reduction in blood concentrations of 25-OH-vitamin D3. Moreover, drugs like phenytoin and carbamazepine have a direct effect on bone metabolism. The risk of developing hip fractures is twice as great in women on chronic antiepileptic treatment compared to controls who do not use these molecules (21). The osteoporotic effects of glucocorticoids, especially for oral and chronic administration, have long been demonstrated in the scientific literature. Glucocorticoids cause bone loss through different mechanisms including reduced calcium absorption by the gut, increased calcium urinary clearance, inhibited production of sex hormones, and reduced bone formation (22).

Prevention of fragility fractures

In order to limit the negative impact of osteoporosis, the international scientific community has been working to identify and develop the most effective strategies to reduce osteoporotic fractures, the main target of osteoporosis treatment. Bone fractures can be prevented through adequate physical exercise, a diet rich in calcium and vitamin D, or dietary supplementation of calcium and vitamin D, and pharmacological treatments aimed at reducing the risk of vertebral, non-vertebral and hip fragility fractures. Different kinds of medication are available for osteoporosis treatment, including antiresorptive agents (e.g. bisphosphonates), which have been used for years to reduce bone resorption in millions of patients, and anabolic drugs (e.g. teriparatide, PTH) to promote bone formation in patients with more severe conditions, although these are not suitable for chronic treatment.

The scientific literature contains different examples of how bone loss and risk of fragility fractures can be reduced in patients with neurological diseases (23).

Whenever possible, immobility should be reduced. In

hemiplegic patients who were able to walk during rehabilitation, a lower BMD loss was observed one year after the stroke event (24). Strategies must also be introduced to limit the consequences of falls in these patients, e.g. femoral protection devices to reduce the mechanical stress induced by falls.

Improving a patient's nutritional state can also be a very beneficial strategy. Improved BMD was reported in post-stroke patients treated with vitamin K2 to promote bone protein matrix formation (25). Moreover, treatment with vitamin D and homocysteine has been reported to reduce fracture risk in stroke patients (26,27).

A number of double-blind, randomised, controlled trials (RCTs) published in recent years have confirmed the reduction of fragility fracture risk in patients with neurological diseases such as Parkinson's disease, stroke or Alzheimer's disease who were treated with risedronate (9,28,29).

Two double-blind RCTs were conducted in Japanese stroke patients, men and women. Risedronate was found to promote bone formation and reduce hip fracture risk in both groups (9,30). In particular, 280 men aged over 65 years with previous stroke were enrolled in the trial for 18 months (Fig. 1). Ten patients in the placebo group experienced hip fracture versus two patients in the risedronate group (OR 0.19, 95% CI 0.04-0.89). The risedronate group was reported to show a significant increase in metacarpal BMD and a reduction of bone absorption markers versus placebo (30). Similar results were obtained in a trial that included 187 elderly women. After 12 months of treatment a significant reduction in hip fracture rates was observed in the risedronate-treated group (1 patient with fracture) versus the control group (7 patients with fracture). Compared to the controls, patients treated with risedronate showed a significant increase in metacarpal BMD and a reduction in bone resorption markers (9).

A RCT conducted on women with Alzheimer's disease gave similar results: a statistically significant reduction in hip fractures in patients treated with risedronate (29) (Fig. 2).

In a recent double-blind RCT, 242 men with Parkinson's disease received risedronate + vitamin D2 (treated group) or vitamin D2 alone (controls). The treated group showed a significant increase in BMD and a reduction in bone resorption markers compared with the controls (28). The number of hip fractures was lower in the risedronate-treated group than in the controls (3 vs 9 patients 95% CI, 0.09 to 1.20). A recently published meta-analysis (23) of RCTs including patients with neurological diseases (Alzheimer's, stroke, Parkinson's) treated with risedronate showed that risedronate led to a 75% reduction of hip fracture risk in patients with at least one neurological condition.

A large clinical programme that included over 16,000 patients (women with postmenopausal osteoporosis or secondary osteoporosis, men with primary or secondary osteoporosis) showed a significant reduction of the risk of vertebral, non-vertebral and hip fractures (31) obtained with risedronate treatment. Moreover, risedronate has been found to be the only bisphosphonate able to reduce the incidence of new clinical vertebral fractures and non-vertebral fractures after only six months of treatment (32,33).

Glucocorticoids have been shown to increase fracture risk after only a few months of treatment; therefore, strategies promoting a rapid reduction of fracture risk are to be recommended in patients with glucocorticoid-induced osteoporosis. A decrease in the risk of vertebral fractures was observed after one year of risedronate treatment in both female and male patients (-70%), thus making risedronate the fastest acting and most effective treatment of glucocorticoid-induced osteoporosis (34).

This particular feature is extremely important since a number of large-scale studies have shown that the risk of new fractures dramatically and rapidly increases in patients with previous fractures. The choice of a highly effective and fast-acting agent thus seems to be strongly advisable. Risedronate is still the only oral bisphosphonate tested in a RCT having prevention of hip fractures as its primary endpoint (35). This trial, in a population of postmenopausal women with previous vertebral fractures, included over 9,000 patients and showed a 60% reduction in hip fracture risk in patients treated with risedronate.

A recent retrospective analysis of the HIP trial demonstrated the hip antifracture efficacy of risedronate even in very elderly patients (>80 years) with osteoporosis (36). Moreover, risedronate is the only oral bisphoshonate available for once-a-day, once-a-week and once-a-month administration (75mg, 2 consecutive days per month) (37), thus offering different options for improving treatment compliance in a broad range of patients.

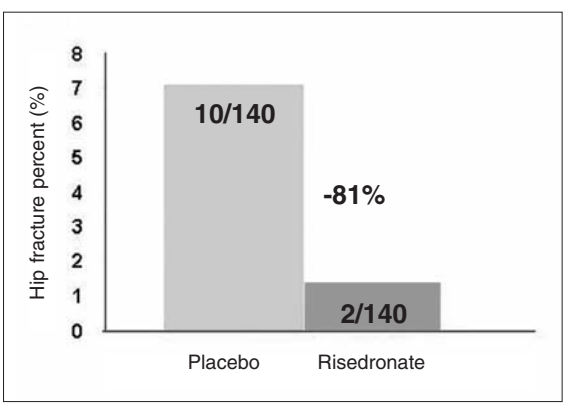

Figure 1 - Risedronate significantly reduces the risk of hip fracture in men following a hemiplegic stroke (30).

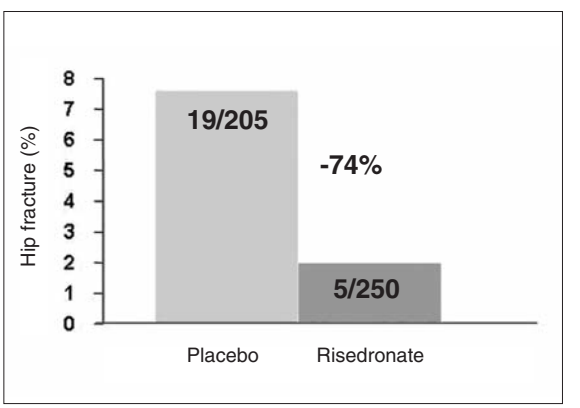

Figure 2 - Significant reduction in the risk of hip fracture with risedronate in women with Alzheimer's disease (29).

Concluding remarks

Patients with neurological diseases such as Parkinson's disease, Alzheimer's disease and stroke are at high risk of developing bone fragility due to bone loss and increased risk of falls. Non-medical strategies are important to reduce the risk of falls and improve nutritional intake in these patients. Risedronate treatment has been demonstrated to reduce fragility fracture risk even in patients (both men and women) with neurological diseases.

References

1. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. Lancet 2002;359:1929-1936
2. Chantraine A, Nusgens B, Lapiere CM. Bone remodeling during the development of osteoporosis in paraplegia. Calcif Tissue Int 1986;38:323-327
3. Kanis JA, Melton LJ 3rd, Christiansen C, Johnston CC, Khaltaev N. The diagnosis of osteoporosis. J Bone Miner Res 1994;9:1137-1141
4. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX™ and the assessment of fracture probability in men and women from the UK. Osteoporos Int 2008;19:385-397
5. Reginster J, Burlet N. Osteoporosis: a still increasing prevalence. Bone 2006;38(Suppl 1):S4-S9
6. Maggi S, Noale M, Giannini S et al. Quantitative heel ultrasound in a population-based study in Italy and its relationship with fracture history: the ESOPO study. Osteoporos Int 2006;17:237-244
7. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int 2006;17:1726-1733
8. Rossini M, Piscitelli P, Fitto F et al. Incidence and socioeconomic burden of hip fractures in Italy. Reumatismo 2005;57:97-102
9. Sato Y, Iwamoto J, Kanoko T, Satoh K. Risedronate therapy for prevention of hip fracture after stroke in elderly women. Neurology 2005;64:811-816.
10. Ramnemark A, Nyberg L, Borssén B, Olsson T, Gustafson Y. Fractures after stroke. Osteoporos Int 1998;8:92-95
11. Kanis J, Oden A, Johnell O. Acute and long-term increase in fracture risk after hospitalization for stroke. Stroke 2001; 32:702-706
12. Ramnemark A, Nilsson M, Borssén B, Gustafson Y. Stroke, a major and increasing risk factor for femoral neck fracture. Stroke 2000;31:1572-1577
13. Melton LJ 3rd, Brown RD Jr, Achenbach SJ, O'Fallon WM, Whisnant JP. Long-term fracture risk following ischemic stroke: a population-based study. Osteoporos Int 2001;12: 980-986
14. Forster A, Young J. Incidence and consequences of falls due to stroke: a systematic inquiry. BMJ 1995;311:83-86
15. Watanabe Y. Fear of falling among stroke survivors after discharge from inpatient rehabilitation. Int J Rehabil Res 2005;28:149-152
16. Mackintosh SF, Hill K, Dodd KJ, Goldie P, Culham E. Falls and injury prevention should be part of every stroke rehabilitation plan. Clin Rehabil 2005;19:441-451
17. Yavuzer G, Ataman S, Süldür N, Atay M. Bone mineral density in patients with stroke. Int J Rehabil Res 2002; 25:235-239
18. Watanabe Y. An assessment of osteoporosis in stroke patients on rehabilitation admission. Int J Rehabil Res 2004; 27:163-166
19. Lloyd ME, Spector TD. Howard R. Osteoporosis in neurological disorders J Neurol Neurosurg Psychiatry 2000;68: 543-549
20. Weller I, Schatzker J. Hip fractures and Alzheimer's disease in elderly institutionalized Canadians. Ann Epidemiol 2004;14:319-324
21. Petty SJ, O'Brien TJ, Wark JD. Anti-epileptic medication and bone health Osteoporos Int 2007;18:129-142
22. Reid DM. Corticosteroid-induced osteoporosis. Clinical Risk 1998;4:7-11
23. Iwamoto J, Matsumoto H, Takeda T. Efficacy of risedronate against hip fracture in patients with neurological diseases: a meta-analysis of randomized controlled trials. Curr Med Res Opin 2008;24:1379-1384
24. Jørgensen L, Jacobsen BK, Wilsgaard T, Magnus JH. Walking after stroke: does it matter? Changes in bone mineral density within the first 12 months after stroke. A longitudinal study. Osteoporos Int 2000;11:381-387
25. Sato Y, Honda Y, Kuno H, Oizumi K. Menatetrenone ameliorates osteopenia in disuse-affected limbs of vitamin D- and K-deficient stroke patients. Bone 1998;23:291-296
26. Sato Y, Asoh T, Kondo I, Satoh K. Vitamin D deficiency and risk of hip fractures among disabled elderly stroke patients. Stroke 2001;32:1673-1677
27. Sato Y, Honda Y, Iwamoto J, Kanoko T, Satoh K. Effect of folate and mecobalamin on hip fractures in patients with stroke: a randomized controlled trial. JAMA 2005;293: 1082-1088 [Erratum in JAMA 2006;296:396]
28. Sato Y, Honda Y, Iwamoto J. Risedronate and ergocalciferol prevent hip fracture in elderly men with Parkinson disease. Neurology 2007;68:911-915
29. Sato Y, Kanoko T, Satoh K, Iwamoto J. The prevention of hip fracture with risedronate and ergocalciferol plus calcium supplementation in elderly women with Alzheimer disease: a randomized controlled trial. Arch Intern Med 2005; 165:1737-1742
30. Sato Y, Iwamoto J, Kanoko T, Satoh K. Risedronate sodium therapy for prevention of hip fracture in men 65 years or older after stroke. Arch Intern Med 2005;165:1743-1748
31. Taggart H, Bolognese MA, Lindsay R et al. Upper gastrointestinal tract safety of risedronate: a pooled analysis of 9 clinical trials. Mayo Clin Proc 2002;77:262-270
32. Roux C, Seeman E, Eastell R et al. Efficacy of risedronate on clinical vertebral fractures within six months. Curr Med Res Opin 2004;20:433-439
33. Harrington JT, Ste-Marie LG, Brandi ML et al. Risedronate rapidly reduces the risk for nonvertebral fractures in women with postmenopausal osteoporosis. Calcif Tissue Int 2004; 74:129-135
34. Canalis E, Bilezikian JP, Angeli A, Giustina A. Perspectives on glucocorticoid-induced osteoporosis. Bone 2004;34: 593-598
35. McClung MR, Geusens P, Miller PD et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 2001;344: 333-340
36. Boonen S, McClung MR, Eastell R, El-Hajj Fuleihan G, Barton IP, Delmas P. Safety and efficacy of risedronate in reducing fracture risk in osteoporotic women aged 80 and older: implications for the use of antiresorptive agents in the old and oldest old. J Am Geriatr Soc. 2004;52:1832-1839
37. Delmas PD, Benhamou CL, Man Z et al. Monthly dosing of 75 mg risedronate on 2 consecutive days a month: efficacy and safety results Osteoporos Int 2008;19:1039-1045