Anti-Osteoporotic Treatment after Hip Fracture

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The role of anti-osteoporotic treatment as part of the secondary prevention after hip fracture in terms of mortality and re-fracture risk has been studied, and the results are promising. Lower mortality after hip fracture is associated with anti-osteoporotic treatment.

anti-osteoporotic treatment | hip fracture | mortality | re-fracture risk

1. Introduction

Hip fracture remains the most important clinical manifestation of osteoporosis, associated with high mortality and morbidity with significant socioeconomic consequences.

Relevant steps were made in the last decade to increase the diagnostic rate of osteoporosis. This pathology's silent character means that the fragility fracture, especially since hip fracture has the noisiest clinical picture, is the first presentation of the disease in a substantial number of cases, regardless of age [1].

It is recognized that a fragility fracture is an essential risk factor for a second fracture [2], with a two times higher relative risk of sustaining a new vertebral or hip fracture after a prevalent fracture. This risk is considered to be higher immediately after the index fracture and decreases with time [3]. Studies demonstrated a linear relationship with age [4]. This effect is more pronounced in the elderly population [4].

The most prominent consequence of hip fracture is the associated higher mortality, which has remained virtually unchanged in the last few decades [5]. Almost a third of these patients will die within one year after a hip fracture [6]. Studies that analyzed the trends in mortality rates after hip fracture showed that the risk decreases with time [6]. The critical period for these patients is the first year after the fracture, with the rates remaining higher even in the following years compared with the general population. Although it is widely accepted that the excess mortality after hip fracture is linked to the pre-fracture comorbid status of the patient and post-fracture complications, studies that adjusted for these factors showed unexplained excess mortality [7].

The secondary prevention of fractures that incorporates medical treatment to improve bone health is essential in breaking the vicious cycle of fragility fracture in these patients. At the same time, most healthcare systems do not succeed in implementing the necessary measures after the first fracture in order to prevent the second one. Only 9–20% of patients receive anti-osteoporotic treatment [8][9][10].

2. Adherence to Treatment

Anti-osteoporotic treatment plays an important role both in the primary and secondary prevention of fragility fractures. Bisphosphonates (BPs) are used as a first-line therapy and are widely recognized as efficient and safe [11]. BPs prevent fractures by increasing bone mineral density (by suppressing bone turnover rates) and are associated with a 40–70% reduction in vertebral and hip fracture rates [12]. Another anti-resorptive agent used is denosumab, a human monoclonal antibody to RANKL, first approved for use in 2010 [13]. Like the BP treatment, denosumab was also proven to effectively prevent osteoporotic fractures, with a significant reduction in vertebral and non-vertebral fragility fractures [14][15]. In Europe, adherence to denosumab is higher compared to that to the BP treatment [16], which is probably explained by the administration mode—denosumab requires only a subcutaneous dose at six months compared to a weekly/monthly administration of oral BP [17]. The authors showed a 24-month persistence with denosumab of 75.1% to 86% with adherence of 62.9% and 70.1%, with lower durability in patients who had at least one fall in the last 12 months and subjects with more comorbidities [16].

In a study that aimed to observe geographic variation in anti-osteoporosis therapy in the UK [18], the authors showed that in 1999, only 5% of hip fracture patients received anti-osteoporosis treatment after the index fracture. Between 1999 and 2004, the percentage increased to 10%, rising spectacularly to 40% between 2005 and 2013. Between 2011 and 2013, a downward trend occurred, with the percentage dropping from 51 to 39% [18].

One study analyzed anti-osteoporotic drug use during four years in Austria [19], covering 98% of the entire population. It showed that only 37.69% of patients with a hip fracture between 2008 and 2010 received anti-osteoporotic treatment, of which 25.9% received BP (18.41% alendronate, 6.49% risedronate, and 5.18% ibandronate). The remaining 62.31% did not receive any anti-osteoporosis treatment one year before and six months after the hip fracture [19]. A higher percentage of women received BP treatment compared to men (30.98% versus 12%). BP was administered before the hip fracture in 20.65% of women compared with 6.11% of men. After the index fracture, 10.34% of women compared to 5.89% of men began treatment with BP, signifying that osteoporosis is underdiagnosed and undertreated in male patients compared to women [19].

3. Mortality

A low bone mass density (BMD) with or without a rapid loss of bone mass was associated with increased mortality risk [20][21]. However, the mechanisms are uncertain considering that, to date, no bone-related factor vital for bone catabolism was demonstrated to affect survival or, inversely, a bone factor that lowers mortality risk independent of fracture risk reduction. An association between a low BMD and a significant risk of cardiovascular mortality and all-cause mortality risk was analyzed [22]. An increased coronary artery calcification seems to correlate with a lower BMD. Both factors are independently associated with the severity of artery calcification on the coronaries with the power to predict mortality [23].

Encouraging news about the anti-osteoporotic treatment being associated with lower mortality rates in osteoporotic patients has been published, and the authors showed increased survival in treated patients [24][25]. A meta-analysis

of 61 randomized controlled trials showed a lower risk of cardiovascular mortality (RR = 0.81, 0.64–1.02, in 10 studies) and a significant reduction in all-cause mortality (RR = 0.90, 0.84–0.98 in 48 studies) with BP treatment [24].

At the same time, a recent comprehensive meta-analysis of randomized placebo-controlled clinical trials published in 2019 [26] suggested that anti-osteoporotic treatment and bisphosphonates particularly were not associated with lower mortality rates. The majority of the included studies in the meta-analysis reported only osteoporotic patients without a fragility fracture [26].

The most significant number of patients covered was 163,273 (all major osteoporotic fractures) in the study of Abtahi et al., recently published in 2020. It showed a 28% lower mortality after hip fracture in current BP-treated patients and, interestingly, a 42% lower mortality after hip fracture in patients with past BP exposure (>1 year) [27] using Cox proportional hazard models.

The HORIZON Zoledronic Acid Once-Yearly Recurrent Fracture Trial One was one of the first studies demonstrating a lower mortality rate after hip fracture associated with anti-osteoporotic treatment [28]. It investigated zoledronic acid [28], with findings that led to the European Union's approval of zoledronic acid treatment in osteoporosis. Other studies published in 2011 [29] and 2014 [30] performed secondary analyses using the patients database from the HORIZON study. The first study mentioned [29] showed lower mortality after 5 mg of zoledronic (HR 0.71, 0.46–1.31 in men and HR 0.74, 0.54–1.02 in women), but with a short median follow-up of 1.9 years. In the second study [30], the authors analyzed zoledronic acid's effect in a subgroup of cognitively impaired patients. A minor difference in mortality rate between the two groups in cognitively impaired patients (23.2% compared to 26.9%) was observed, as well as lower mortality rates in the treatment arm (6.2% compared to 10.5% in the placebo arm, $p < 0.001$). Another secondary analysis of the HORIZON study [31] showed a lower relative risk of pneumonia or a lower respiratory infection associated with bisphosphonate therapy, although not statistically significant ($p > 0.05$). Risk and mortality after pneumonia were significantly lower in bisphosphonate-treated patients compared to naive patients but also when compared to other anti-osteoporosis treatments [32].

Teriparatide was the pro-osteogenic agent investigated. Most of the studies regarding teriparatide and hip fracture are related to secondary outcomes such as accelerated fracture healing and union, with less data regarding mortality or subsequent fractures [33]. The meta-analysis regarding the effect of teriparatide included in the review showed data from two clinical trials and three retrospective cohort studies [33], with a total of 607 patients. The model showed no significant effect on mortality or subsequent fracture risks [33]. The most important limitation is the lower heterogeneity between included studies, related to the inconsistencies between treatment doses and duration [33].

The most valuable initiation time for anti-osteoporotic treatment (before or after the index fracture) in terms of lower mortality rates is not precise, with studies such as Behanova et al. [34] and Brozek et al. [19] showing that initiation after the index fracture is more effective than before the fracture. Although the studies presented included large

numbers of patients, perhaps because of the low adherence and compliance, even more significant numbers are needed to validate the actual results.

The mechanism through which the BP treatment influences mortality is still poorly understood. The effects on the accelerated bone turnover [35], the anti-inflammatory effect [36], or the modulation of pro-inflammatory cytokines [37] have been stipulated as possible mechanisms.

4. Second Fracture

It is well known that a prevalent fragility fracture almost doubles the risk of a second fracture [2]. The high mortality associated with hip fracture is even higher in patients who suffer recurrent fractures [38]. A link between the lower mortality after hip fracture in patients with anti-osteoporotic treatment and subsequent lower risk of re-fracture was searched and investigated.

After eight years of follow-up, a prospective cohort study found a lower risk for subsequent fractures (HR 0.60, 0.49–0.73) in treated patients included in Fracture Liaison Services (FLS). Other medical interventions included in addition to anti-osteoporotic treatment can explain in part this association [39]. The FLS implementation was not correlated with a decreased risk of second fractures [40]. All new fractures were recorded in patients not treated in a group multicenter prospective study that investigated the results of implementing FLS in Greece [41].

Another population-based cohort study [42] that included 88,320 hip fracture patients found a statistically significant correlation between re-fracture rate and alendronate treatment, also related to the medication possession ratio (MPR).

Although new data showed that anti-osteoporotic treatment does not have an effect on mortality in osteoporotic patients [26], data regarding only hip fracture patients are still scarce and insufficient. The excess mortality in hip fracture patients [43] compared to osteoporotic individuals without fracture is an important argument to continue the research for possible beneficial effects for this category. The increased trends of hip fracture incidence worldwide [44] and the relatively unchanged mortality rates in the last few decades [5] in hip fracture patients further necessitate the search for possible treatment benefits.

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