

Atypical Osteoporotic Fractures: Impact on Therapeutic Decision Making in Osteoporosis

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Osteoporosis is an important public health problem affecting millions of people worldwide. Fragility fractures are its major clinical manifestation. In Caucasian populations, about 50% of women and 20% of men older than 50 years will sustain an osteoporotic fracture in their remaining lifetime. As the population ages, the prevalence of osteoporosis increases [1]. Therapeutic efforts are aimed at fracture prevention. Most current therapies for osteoporosis are anti-resorptive, which inhibit osteoclastic bone resorption but do not promote bone formation. These treatments were proven in randomized clinical trials of 3 years duration to be efficacious in reducing the risk of osteoporotic fractures in postmenopausal osteoporotic women with no major comorbidities. Four extension trials were conducted, with reduced sample size, for 6 to 10 years [2-5]. They were not powered to assess fracture risk reduction; however, in post hoc analysis, some fracture risk-reducing benefits of long-term treatment with alendronate were observed for patients who entered the extension study with low femoral neck bone mineral density (T score below -2.5) and without vertebral fractures. Similar findings were observed with zoledronate [3,5].

In real life, patients who are treated with anti-resorbing agents often have

comorbidities with various degrees of severity. Treatment duration lasts for many years, occasionally exceeding a decade (alendronate was approved for clinical use in 1996).

Atypical fractures – a possible severe complication of long-term treatment with potent anti-resorbing agents – have gained medical attention after initial case reports and small series. Atypical fractures [6-8] located in the subtrochanteric region and diaphysis of the femur have been reported in patients taking bisphosphonates and in patients on denosumab, but may also occur in patients with no exposure to these drugs, suggesting a possible background risk of atypical fractures in osteoporotic patients. Individuals may have a genetic risk of developing this complication that is yet unknown [9,10].

Rosenthal et al. [11], in this issue of *IMAJ*, report two cases of subtrochanteric atypical fractures related to bisphosphonate treatment, both occurring after prolonged use. The first patient was a 68 year old woman with multiple comorbidities – diabetes mellitus type II, asthma and depression – that may have contributed to increased osteoporotic fracture risk as well as to atypical fracture risk. No prior fracture history, bone density data or concomitant medications were reported. The patient was treated for 7 years with risedronate, a bisphosphonate with apparently shorter skeletal retention time.

The second patient was a 73 year old woman whose treatment included several consecutive agents with increasing anti-resorbing potency: 6 years of treatment with raloxifene (a mild anti-resorbing agent, with no skeletal accumulation; atypical fractures were not reported with

its use), followed by 4 years of treatment with alendronate, followed by intravenous zoledronic acid. The reason for these consecutive treatments was not mentioned. The patient sustained an osteoporotic fracture of L2 vertebra 6 months prior to the atypical femoral fracture.

These cases pose several questions for therapeutic decision making in osteoporosis, especially for long-term treatment, in the light of the risk of the devastating complication – atypical fracture. The issue of atypical fractures was addressed by the ASBMR task force, which recently published its updated report [10]. The report contains an update on epidemiological, etiological, diagnostic and therapeutic issues of atypical fracture. It supports the notion that these fractures are a form of stress or insufficiency fractures. In addition, the evidence for an association with long-term bisphosphonate therapy is considerably stronger than it was at the time of the 2010 report [9] and is based on several different types of studies, including a meta-analysis.

Bisphosphonates, the most frequently used anti-fracture treatment, have a very long skeletal retention time. The calculated terminal half-life of elimination from the skeleton can be as long as 10 years [12]. The slow release of bisphosphonates from the skeleton is probably responsible for the slow speed of the reversal of their effect on bone after treatment is stopped. No studies have assessed the anti-fracture efficacy of bisphosphonates after treatment discontinuation; however, since their therapeutic effect is mainly attributed to reduction of bone turnover, this cumulated

ASBMR = American Society for Bone and Mineral Research

effect might preserve anti-fracture efficacy. The findings of a post hoc analysis of the HORIZON study that demonstrated a reduction in fracture risk for up to 3 years after a single infusion of zoledronic acid [13] support this assumption.

On the other hand, prolonged bisphosphonate use harbors a risk of atypical fracture. Although the relative risk of patients with such fractures taking a bisphosphonate is high, ranging from 2.1 to 128, the absolute risk is low, ranging from 3.2 to 50 cases per 100,000 person-years. However, long-term use may be associated with more than doubling of this risk (~100 per 100,000 person-years) [13]. Bisphosphonates localize in areas where stress fractures develop; suppression of targeted intracortical remodeling at the site of an atypical fracture could impair the processes by which stress fractures normally heal. Withdrawal of the drug may decrease the risk of atypical fractures.

It is clearly evident that the benefits of anti-remodeling agents for preventing common osteoporotic fractures outweigh the relatively small risk of atypical fractures. Nonetheless, recognition of these risks should prompt physicians to target therapy towards patients at high risk of fractures and to consider the optimal duration of therapy with potent anti-remodeling agents, e.g., bisphosphonates or denosumab. Treatment should be initiated only after weighing the risks and benefits for an individual patient and not based solely on the BMD criterion. Introduction of new risk assessment tools such as FRAX (this country-specific tool is currently being assessed for Israel), which combines clinical risk factors with bone densitometry, the use of bone turnover markers for risk assessment, and careful patient follow-up during bisphosphonate treatment may lead to more efficient risk stratification strategies. This, in turn, will result in improved selection of patients for a prolonged anti-resorbing treatment or a shorter therapeutic intervention with a subsequent follow-up [14].

The contribution of non-drug-related interventions such as improvement of muscle strength and fall prevention strategies, by means of physical activity [15-17], vitamin D replenishment [18], and adequate calcium intake is worth keeping in mind. These interventions can be offered to low risk patients as an initial therapeutic strategy, thus decreasing fracture risk without generating risk of atypical fractures. They should also be a part of all medical interventions in high risk osteoporotic patients.

Switching from a weaker anti-resorbing agent to another, for example from raloxifene to a long-term bisphosphonate, and later to a more potent anti-resorber like zoledronate (case 2 in Rosenthal's study) often following minor BMD changes (less than the least significant difference or greater changes that may be due to technical densitometric issues), may harbor a potential increase in the risk of atypical fractures in susceptible individuals that we cannot detect in advance. There is increasing evidence that a follow-up of BMD changes in individual patients (contrary to large group assessment in clinical trials) contributes little to therapeutic response evaluation, since even in the research setting BMD explained only 4%–24% of the therapeutic effect of anti-resorbing agents [19]. For example, treatment with raloxifene induced minor BMD increases, below the least significant difference for BMD change in an individual patient, with a concomitant significant 40% risk reduction in spinal fractures. It is possible that patients' follow-up using serum bone turnover markers (CTX and P1NP) during anti-resorbing treatment will be more beneficial in a clinical setting than repeated BMD measurements, which may guide treatment duration and short-term or permanent discontinuation of bisphosphonates.

The use of anabolic agents to treat osteoporosis is worth considering. At present the only efficient anabolic agent is teriparatide. It was shown to increase bone formation and improve bone micro-architecture, with a concomitant significant decrease in fracture risk in high risk osteoporotic patients [20]. In Israel, this expensive medication

is reimbursed for patients who sustained a fracture during anti-resorbing treatment. Occasionally patients are offered potent injectable anti-resorbing agents under such circumstances, thus potentially increasing the risk of atypical fractures. This might be the case with the second patient in the article by Rosenthal et al. The patient remained on anti-resorbing treatment after sustaining an L2 osteoporotic fracture during prolonged bisphosphonate treatment. Switching to anabolic treatment might have been beneficial in this case. Another issue clearly demonstrated by this case is that, unfortunately, there is at present no proven medical treatment that can speed up prolonged atypical fracture healing, although there is anecdotal evidence that teriparatide may advance it. This treatment may be offered to patients with delayed healing of an atypical fracture.

In summary, in the last few decades the medical community was trained to treat according to evidence-based medicine; however, real-life clinical practice patients differ from the carefully selected population of the interventional double-blind placebo-controlled trials, and many of the "real-life" patients would not have qualified to participate in these studies due to comorbidities and concomitant medications. Evidence on efficacy and safety of long-term anti-resorbing treatment is limited. When deciding on the therapy, its duration, and switching from one treatment to another, clinical judgment should be applied to each individual.

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BMD = bone and mineral density

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Capsule

Cancer cell profiling by barcoding allows multiplexed protein analysis in fine-needle aspirates

Immunohistochemistry-based clinical diagnoses require invasive core biopsies and use a limited number of protein stains to identify and classify cancers. Ullal et al. introduced a technology that allows analysis of hundreds of proteins from minimally invasive fine-needle aspirates (FNAs), which contain much smaller numbers of cells than core biopsies. The method capitalizes on DNA-barcoded antibody sensing, where barcodes can be photocleaved and digitally detected without any amplification steps. After extensive benchmarking in cell lines, this method showed high reproducibility and achieved single-cell sensitivity.

The authors used this approach to profile ~90 proteins in cells from FNAs and subsequently map patient heterogeneity at the protein level. Additionally, they demonstrated how the method could be used as a clinical tool to identify pathway responses to molecularly targeted drugs and to predict drug response in patient samples. This technique combines specificity with ease of use to offer a new tool for understanding human cancers and designing future clinical trials.

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Capsule

Immunological and virological mechanisms of vaccine-mediated protection against SIV and HIV

A major challenge for the development of a highly effective AIDS vaccine is the identification of mechanisms of protective immunity. To address this question, Roederer and co-authors used a non-human primate challenge model with simian immunodeficiency virus (SIV). The authors show that antibodies to the SIV envelope are necessary and sufficient to prevent infection. Moreover, sequencing of viruses from breakthrough infections revealed selective pressure against neutralization-sensitive viruses; they identified a two amino acid signature that alters

antigenicity and confers neutralization resistance. A similar signature confers resistance of human immunodeficiency virus (HIV)-1 to neutralization by monoclonal antibodies against variable regions 1 and 2 (V1V2), suggesting that SIV and HIV share a fundamental mechanism of immune escape from vaccine-elicited or naturally elicited antibodies. These analyses provide insight into the limited efficacy seen in HIV vaccine trials.

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