Editorial

Denosumab and atypical femoral fractures

Stress fractures of the femoral shaft or subtrochanteric region (atypical femoral fractures) are clearly associated with bisphosphonate use. This association is stronger than the one between smoking and lung cancer. Still, provided a patient has osteoporosis and is not too old, a few years of bisphosphonate treatment will reduce the total risk of fracture, because the reduction in the absolute risk of osteoporotic fracture is greater than the increase in the risk of stress fracture.

In this issue of Acta Orthopaedica, we publish a report on a patient with bilateral atypical fractures while under treatment with denosumab, another type of antiresorptive drug. Based on the mechanism of action, one could speculate that denosumab may be associated with a similar risk of atypical fracture as most bisphosphonates. The risk could also be higher, or lower.

Denosumab is an antibody that blocks the formation of osteoclasts. For several months after injection, osteoclast numbers are greatly reduced and there is virtually no resorption going on at all. Bisphosphonates bind tightly to bone surfaces shortly after dosing, and any unbound bisphosphonate is quickly eliminated from the body. The bisphosphonate reaches the intracellular compartment first when an osteoclast ingests bisphosphonate-containing bone. The intracellular bisphosphonate is toxic and will inactivate the osteoclast. While bisphosphonates are only in circulation shortly after dosing, denosumab remains in the blood for months.

Stress fractures are thought to start by accumulation of microscopic cracks. Such crack formation is a part of bone physiology. Normally, areas with microcracks are resorbed by osteoclasts and replaced with new bone by a process called "targeted remodeling". If targeted remodeling is disturbed by antiresorptive treatment, microcracks might grow, fuse, and cause stress fractures. The osteoclasts are steered to the area where microcracks accumulate by RANKL, which is released by osteocytes residing at the site. RANKL is the very molecule blocked by denosumab.

Microcracks tend to accumulate in old bone that is unlikely to contain bisphosphonate, because bisphosphonates bind to the bone surface, and the old bone was formed and embedded before treatment started. Thus, if bisphosphonates are to disturb targeted remodeling, they must somehow reach the site, inside the bone. Only doses administered while targeted remodeling is going on will have this possibility. Sites with ongoing resorption also have an increased affinity for bisphosphonates in the circulation. The important role of ongoing treatment, rather than skeletal accumulation of bisphosphonates, is further supported by the observation that the risk of atypical fracture diminishes rapidly after cessation of treatment. (In contrast, the reduction in risk of osteoporosis fracture seems to remain for years). This theory about ongoing treatment and atypical fracture is not falsified by the continuously increasing risk during long-term bisphosphonate treatment. The increase can be explained by an accumulation of areas with microdamage as long as targeted remodeling is inhibited.

Accordingly, denosumab and weekly administration of bisphosphonates will both influence targeted remodeling, while bisphosphonates given once a year will only reach those areas of microdamage that are undergoing remodeling at the very time point of the injection. If the pathophysiological model suggested here is appropriate, bisphosphonates administered once a year should confer a lower risk of atypical fractures. On the other hand, with denosumab, the ability to resorb bone usually recovers—at least partially—towards the end of the interval between injections. This might be sufficient for the skeleton to deal with areas of microdamage.

Finally, bisphosphonates are only weakly efficacious in areas with a pathologically increased resorptive activity. This is easily conceived, considering that each osteoclast will resorb some bone before it is inactivated by ingested bisphosphonate, and if new osteoclasts are continuously recruited, the bone will finally be lost. In contrast, denosumab blocks osteoclast recruitment and is therefore probably more efficacious for e.g. reducing bone loss around loose prostheses.

In conclusion, it appears likely that denosumab confers a similar risk of atypical fracture as e.g. oral alendronate, through its effect on targeted remodeling. Perhaps once-yearly bisphosphonates have a lower risk. The possibility of a stronger effect of denusomab on bone resorption at sites with increased recruitment of osteoclasts could mean a higher risk of atypical fracture. Conversely, the recovery period between denosumab injections could mean a lower risk. However, atypical fractures are uncommon, and with a correct indication (but only then), antiresorptives prevent many more fractures than they cause.

Per Aspenberg
Per.Aspenberg@liu.se

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