DOI: http://doi.org/10.4038/sjdem.v13i2.7486

New advances in the treatment of post-menopausal osteoporosis

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John Hunter, a British surgeon, first discovered osteoporosis in the 1800s, a condition that predominantly affects post-menopausal women. Over the years the perception of post-menopausal osteoporosis (PMO) has changed from an inevitable consequence of aging and menopause to a chronic treatable non-communicable disease. Oestrogens emerged as the first treatment option for PMO more than 70 years ago. Bisphosphonates were introduced in the 1970s as an effective treatment option for PMO and since then have become the mainstay of therapy. Invent of denosumab was an important juncture in PMO treatment as it offered superior efficacy with lesser adverse effects over bisphosphonates. Since then, many new agents have been added to the therapeutic armamentarium of osteoporosis treatment and the most recent attention is on developing newer and more efficacious anabolic therapy. Since the use of anabolic therapy is only indicated for a maximum of 1-2 years due to safety and efficacy issues, sequential approach where anabolic therapy is followed by a antiresorptive therapy (bisphosphonates or denosumab) has become the preferred approach in treating PMO.

The nitrogen-containing bisphosphonates including alendronate,zoledronate, risedronate, & ibandronate are analogues of inorganic pyrophosphate. They bind to bone hydroxyapatite and promote inhibition and apoptosis of the osteoclasts [1]. This leads to the inhibition of bone resorption and increases in bone mineral density (BMD). There is data to suggest that osteoclast inhibition may even continue following the cessation of bisphosphonates [2].The long term usefulness of bisphosphonates in treating PMO is somewhat limited as the fracture prevention effect of bisphosphonates seems to reach a plateau after several years of treatment and their long-term use is associated with atypical femoral fractures [3,4]. Denosumab, a monoclonal antibody against the Receptor activator of nuclear factor-kappa B ligand (RANKL), has shown a continuous effect on BMD increase. Vertebral and non-vertebral fractures were shown to reduce over 10 years of its continuous use[5]. Since denosumab doesn't accumulate in the bones like bisphosphonates, a rapid loss of BMD followed by an increase in the number of fractures was seen after its discontinuation. Therefore, the use of other antiresorptive agents is recommended once denosumab is discontinued.

Subcutaneous injections of teriparatide given for a maximum period of 24 months have been shown to increase lumbar BMD and prevent vertebral and non-vertebral fractures [6]. The recent Denosumab and Teriparatide Administration (DATA) study indicated that the combination of denosumab and teriparatide shows a superior effect on BMD than each agent given alone [7]. However, the DATA switch study indicated that when teriparatide is given after denosumab treatment, it leads to transient bone loss in contrast to teriparatide being given first where it is shown a continuous improvement in BMD in the spine and femoral neck [8]. These data suggest the importance of the timing of anabolic therapy when used in sequential therapy in post-menopausal osteoporosis. Abaloparatide is a synthetic analog of PTH-related protein is another recently approved anabolic therapy similar to teriparatide. In clinical studies, abaloparatide has shown a superior anti-fracture effect with less preponderance hypercalcemia when compared to teriparatide [9].

The recent discovery that the Wnt pathway and its inhibitors sclerostin and Dickkopf (DKK)-1 play a key role in the central regulation of bone metabolism has led to focusing attention on these molecules to develop new therapy for osteoporosis [10]. Romosozumab, a monoclonal antibody that acts by inhibiting sclerostin has a dual mode of action and increase bone formation and suppress bone resorption. Given the impressive results shown by romosozumab compared to other agents currently in use, in BMD increase and fracture reduction, it is likely to become a major therapeutic option for the

treatment of PMO [11]. Other sclerostin inhibitors and DKK-1 inhibitors are currently under development. In preclinical studies, dual inhibition of sclerostin and DKK-1 has shown results that were not considered possible before with a single agent and offer a promising new treatment strategy for the future [12].

World osteoporosis day is commemorated on the 20th of October each year, to draw public attention to this silent yet so devastating chronic bone disease. Amidst the exciting new developments in the treatment of osteoporosis, still there are treatment gaps that need to be filled to deliver the optimum care for patients with PMO.

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