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EDITORIAL

Therapy for musculoskeletal disorders

In their mini-review in this issue of the Journal of Orthopaedic Translation (JOT), Cecchi and colleagues describe the signalling pathways that bone morphogenetic protein 7 (BMP-7) uses to exert its effect on bone, as well as its efficacy to promote fracture healing [1]. Thanks to supportive preclinical and clinical data, rhBMP-7 (also known as osteogenic Protein-1) has received approval from the Food and Drug Administration and it is now commercially available. Donor-site morbidity, volume constraints, and infection commonly associated with autogenous bone grafting (ABG) has made rhBMP-7 an attractive alternative for the stimulation of bone formation, particularly in the nonunion of bone, where recent studies indicate similar efficacy to ABG. Also of interest in this context, the combination of rhBMP-7 with ABG has been studied and found to show higher rates of fracture healing than either method alone [2].

Antisclerostin antibodies, a novel promising treatment option for osteoporosis

Also in this issue of JOT, you will find several articles with a focus on novel anti-osteoporotic treatment options. The review article written by Suen and Qin is dedicated to sclerostin [3], a bone anabolic treatment that is perhaps the most promising emerging therapeutic target for the treatment of osteoporosis and osteoporotic fracture. At present, osteoanabolic therapy is limited to the use of parathyroid hormone 1—84 (PTH [1—84]) and its biologically active 34-residue amino-terminal fragment known as teriparatide (PTH [1—34]). When administered intermittently (once daily), these PTH molecules are osteoanabolic [4,5]. However, PTH has certain disadvantages such as the need for daily self-injections, high cost, requirement for refrigeration, a 2-year limit to its use and the US FDA-mandated boxed warning concerning osteosarcoma in rats in preclinical toxicity studies [6]. Furthermore, the increase in bone formation seen with PTH treatment is often followed by an increase in bone resorption, resulting in an 'undesired' increase in bone remodelling. The development of other classes of osteoanabolic drugs, such as the antisclerostin antibodies described by Suen and Qin [3], which, in contrast to PTH, are associated with a reduction in bone resorption, is thus highly desirable. Results from a randomized, double-blind, placebo-controlled multicentre Phase 2 clinical trial of blosozumab, a humanized monoclonal antibody targeted against sclerostin, in postmenopausal women with low bone mineral density (BMD) were reported recently [7]. Injections of blosozumab for 1 year resulted in substantial anabolic effects on the skeleton and were well tolerated. These results were similar to those reported earlier for romosozumab (AMG 785) [8,9]. Further evaluation of the efficacy of these agents including fracture end-points, and of their safety in large Phase III controlled studies are eagerly awaited. The transition from PTH to antisorptive therapy after 2 years is predicated on FDA and other national regulations limiting its use to this period of time. In analogy, for antisclerostin antibodies, sequential treatment to follow the osteoanabolic treatment with an antiresorptive drug for long-term preservation seems an attractive possibility.

The problem with available long-term treatment options for osteoporosis

Currently, no treatment can completely reverse established osteoporosis and all available antiresorptive treatment options are limited in the duration of their use. Early intervention can prevent osteoporosis in most people. For patients with established osteoporosis, medical

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intervention can halt its progression. If secondary osteoporosis is present, treatment for the primary disorder should be provided. Therapy should be individualized based on each patient's clinical scenario, with the risks and benefits of treatment discussed between the clinician and patient [10]. According to a clinical practice guideline by the American College of Physicians, because of the significant disability, morbidity, mortality, and expenses associated with osteoporotic fractures, treatment is aimed at fracture prevention [11]. Guidelines for osteoporosis treatment are also available from the American Association of Clinical Endocrinologists [12] and from a combined effort undertaken recently by the International Osteoporosis Foundation and European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis [13]. Preventive measures include modification of general lifestyle factors, such as increasing weight-bearing and muscle-strengthening exercise, which have been linked to fractures in epidemiologic studies, and ensuring optimum calcium and vitamin D intake as an adjunct to active antifracture therapy [14]. Medical care includes the administration of adequate calcium, vitamin D, and anti-osteoporotic medication such as bisphosphonates, the Receptor Activator of NF-κB Ligand (RANKL) inhibitor denosumab (Dmab), parathyroid hormone, raloxifene, strontium ranelate and until recently, oestrogen [12,13]. A substantial number of different treatment options have become available, raising the question as to whether or not additional efforts should still be undertaken to develop novel strategies for intervention? One of the challenges of the currently used antiresorptive treatment options is that for reasons of safety, or lack of long-term antifracture data, they are all limited in their duration of use. This may provide an opportunity for strategies presented in this issue of JOT (Su et al [15]; Luo et al [16]; Chen et al [17]) which are all based on Chinese traditional herbal medicines. So what are the limitations of existing antiresorptive therapies that these alternative treatment options would have to overcome, and what are the gaps that must be filled before they can be recommended for widespread clinical use in osteoporosis?

Bisphosphonates are the mainstay of osteoporosis therapy with robust data from numerous placebo-controlled trials demonstrating efficacy in fracture risk reduction over 3—5 years of treatment [18]. Although bisphosphonates are generally safe and well tolerated, concerns have emerged about adverse effects related to their long-term use. Specifically, the continued use of bisphosphonates after 5 years is associated with an increased risk of otherwise rare atypical femoral fractures (AFF), osteonecrosis of the jaw (ONJ), and oesophageal cancer. The incidence of ONJ is greatest in the oncology patient population (1—15%), where high doses of these medications are used at frequent intervals [19]. In contrast, in the osteoporosis patient population, the incidence of ONJ is estimated at 0.001% to 0.01%, marginally higher than the incidence in the general population (<0.001%). Recently, ONJ has been identified in bisphosphonates-naïve patients receiving Dmab [20], which necessitated accommodation of Dmab in the definition. Although an association between bisphosphonates or Dmab use and ONJ seems likely, a causal relationship with bisphosphonate or Dmab therapy has not been established [19]. Another concern is that studies with radiographic review consistently report significant associations between AFFs and bisphosphonates use, even though the strength of associations and magnitudes of effect vary [21]. The absolute risk of AFFs in patients on bisphosphonates is low, ranging from 3.2 to 50 cases per 100,000 person-years. However, long-term use may be associated with higher risk (100 per 100,000 person-years). Bisphosphonates appear to localize in areas that are developing stress fractures. It has been hypothesized that suppression of targeted intracortical remodelling at the site of an AFF could impair the processes by which stress fractures normally heal. In support of this hypothesis, when bisphosphonates are stopped, risk of an AFF may decline.

Concerning long-term efficacy of bisphosphonates, examination of studies where bisphosphonates had been administered for at least 3 years, and for which fracture data were compiled, revealed that bone mineral density at the femoral neck and lumbar spine was maintained but without a consistent reduction in fracture rate [22]. Taken together, these findings led the FDA to issue revised recommendations for the use of these drugs after 3 to 5 years [23,24]. The new FDA recommendation indicated in revised labelling states that, "the optimal duration of use has not been determined. The need for continued therapy should be re-evaluated on a periodic basis." However, no specific limits on the duration of treatment were imposed. The FDA review noted that "there is no agreement on the extent to which cumulative use of bisphosphonates increases the risk" of atypical fractures.

Because bisphosphonates accumulate in bone with some persistent antifracture efficacy after therapy is stopped, it is reasonable to consider a 'drug holiday'. There is considerable controversy regarding the optimal duration of therapy and the length of the holiday, both of which should be based on individual assessments of risk and benefit [18]. It is against this background that the idea to replace strong suppressors of bone remodelling such as bisphosphonates or the RANKL inhibitor Dmab with less strongly active drugs for long-term management of osteoporosis patients may become an attractive alternative to simply stopping treatment and leaving patients exposed to an increased fracture risk.

The 'mild' alternatives to strong antiresorptives for long-term treatment of osteoporosis?

In this issue of JOT, two 'milder' treatment options, namely extracts from *Alpinia officinarum* (AOH) (Su et al [15]) and *Epimedii Folium* (Chen et al [17]), that are used in traditional Chinese medicine are presented, which may provide an alternative for long-term treatment of osteoporosis patients. In their study in ovariectomized rats (OVX), Su and colleagues [15] demonstrated that extracts of AOH exerted a mild antioxidant effect, increased bone formation and showed mild antiresorptive properties. Partial reversal of bone loss was achieved, and it remains to be seen whether it is possible to optimize the extraction procedure to enrich the active ingredients in order to achieve a more pronounced effect on bone, while maintaining the favourable

profile on the uterus. In a direct comparison of Xian Ling Gu Bao (XLGB) capsules containing two different *Epimedium* species, namely *Epimedium pubescens* (XEP) or *Epimedium koreanum* (XEK), Chen et al [17] reported that both XLGB capsules were equally effective for the prevention of oestrogen-depletion induced osteoporosis in a rat OVX model. *In vitro* results suggested that all of the six compounds contained in XEP and XEK might contribute to the antiosteoporotic effects of the two XLGB formulae and result in a comparable efficacy of XEP and XEK. In line with a previous report, epimedin C was identified as the main component of XEP, while icariin is the main flavonoid in XEK. It should be noted that the use of XLGB capsules was officially approved by the Chinese State Food and Drug Administration as an over-the-counter drug for the treatment of osteoporosis, osteoarthritis, aseptic osteonecrosis, and fractures. In the first ever multicentre and randomized clinical trial of herbal Fufang, daily oral XLGB was safe in postmenopausal women when administered over a 1-year treatment period [25]. Patients ($n \sim 50$) treated with XLGB demonstrated a statistically significant but mild increase in dual-energy X-ray absorptiometry BMD at the lumbar spine at 6 months, and a numerically increased BMD at 12 months. However, there was no dose-dependent response. Also, bone turnover marker levels declined during the first 6 months after XLGB treatment, a difference no longer observed at 12 months. There was no significant difference in the overall incidence of side effects among treatment and control groups. In spite of these encouraging results, future clinical studies with longer duration will be required to address the question raised by the biphasic BMD response and transient effects of Fufang on bone turnover markers [25]. Study endpoints will have to include the clinical examination of oestrogen-dependent tissues as well as fractures as a study endpoint before this herbal medicine can be recommended for the prevention or treatment of osteoporosis [26].

Also in this issue of JOT, Luo et al [16] describe the effect of tanshinol, a polyphenolic water-soluble component of the traditional Chinese medicine *Salvia miltiorrhiza Bunge*. When tested in larval zebrafish, tanshinol stimulated bone formation and attenuated dexamethasone-induced inhibition of osteogenesis. The authors provide evidence that tanshinol protects organisms against oxidative stress elicited by dexamethasone via scavenging of excessive accumulation of reactive oxygen species generation, and simultaneously attenuates the inhibitory effect of dexamethasone on osteoblastic differentiation and mineral formation. In a previously published study, Cui et al showed that salvianolic acid B, a polyphenolic component of *Salvia miltiorrhiza Bunge*, prevented bone loss in prednisone-treated rats through stimulation of osteogenesis and bone marrow angiogenesis [27]. Like AOH, salvianolic acid B seems to combine antioxidant effects with mild antiresorptive and bone formation stimulating properties.

Eventually, improved preparations of herbal medicines will have to be tested to establish their safety, before clinical trials can be initiated to establish an active dose and test their antifracture efficacy in adequately powered Phase 3 trials [26]. In the absence of proven antifracture efficacy, it is unlikely that herbal medicines will gain widespread use in the treatment of osteoporosis, either as stand-alone long-term treatment options or for the preservation of bone following withdrawal from anabolic therapy with PTH or antisclerostin antibodies.

Finally, reported in this issue of JOT, Kamer and colleagues [28] computed 3D statistical bone and averaged bone density models with low, middle and high total vBMDs, using an extended, standard high-resolution peripheral quantitative computed tomography (HR-pQCT) protocol to image intact postmortem samples of the proximal humerus. 3D patterns of the size and shape variations were analysed using principal component analysis in addition to the vBMD distributions and variabilities using volume rendering and virtual bore probing. New anatomical 3D data is expected to improve our understanding of the normal bony anatomy of the proximal humerus. In addition, the extended HR-pQCT protocol and computer models proposed by Kamer et al [28] might be used for other skeletal sites and serve as 3D reference models that can be applied to systematically improve implant design and anchorage.

Conflicts of interest

Dr. Gasser is an employee of the Novartis Institute for BioMedical Research.

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