EXPERT OPINION

Drugs for bone healing

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Introduction: The biological process of fracture healing is complex with influences that are both patient-dependent and related to the trauma experienced and stability of the fracture. Fracture healing complications negatively affect the patient's quality of life, even more when fractures occur in the elderly osteoporotic patients.

Areas covered: In the polytherapy for bone regeneration, a high success rate was obtained with the use of growth factors, osteogenic cells, and osteoconductive factors. There have been high expectations that treatment with drugs active on bone remodeling would be efficient for acceleration of fracture healing. A literature search was undertaken using wording like "drug or pharmacology of fracture healing." This report will review the systemic pharmacological agents for which clinical trials documenting their efficacy on bone healing have been carried out or are underway.

Expert opinion: At present the use of systemic pharmacological agents to enhance fracture healing in the clinical setting is still controversial. However, future clinical trials will offer the possibility to obtain data that will make possible the registration of a drug as a "healer."

Keywords: anabolics, antiresorptives, anti-sclerostin antibody, bone formation, bone healing, bone morphogenetic proteins, growth factors, parathyroid hormone peptides, strontium ranelate

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1. Introduction

Fractures greatly impair the quality of life of the affected patients and this is even more true if complications exist in the normal healing process [1]. Bone has an innate capacity for repair and regeneration in response to injury. Both processes encompass integrated mechanisms where cells, local factors, and the extracellular matrix work together to restore the continuity of the injured bone tissue and the formation of new bone tissue. This well-orchestrated process results at the end with the restoration of function of the fractured bone segment.

Bone regeneration is a physiological process involved in continuous remodeling throughout adult life, as well demonstrated for a tissue that is completely renewed about every 10 years in adults [2]. However, there are complex clinical conditions in which bone regeneration is required in large quantity, such as for skeletal reconstruction of large bone defects created by trauma or cases in which the normal regenerative process is compromised, including osteoporosis.

Both the repair and regeneration processes are controlled by an array of complex cellular and molecular mechanisms that involve local and systemic factors that act on the recruitment and differentiation of many cell types involved with fracture healing [3-6]. Fracture healing is driven by the activities of local bone mediators, including the transforming growth factor beta (TGFbeta) superfamily of morphogens and angiogenic molecules, whose temporal pattern of expression has been well characterized. With improved understanding of fracture healing and bone regeneration at the molecular level, a number of key molecules that regulate this complex physiological process have been identified, and are already in clinical use or under investigation to enhance bone repair [7].

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Article highlights.

The paper covered the following key aspects related to bone healing:

- Systemic pharmacological control of bone healing.
- Role of osteoporosis in influencing fracture repair.
- Clinical evidences related to bone antiresorptive agents.
- Clinical evidences related to bone-forming agents.
- Mechanisms of action of bone remodeling active drugs on bone regeneration.

This box summarizes key points contained in the article.

Application of the "orthobiologics" concept helps to translate the knowledge accumulated in the molecular mechanisms of bone regeneration to clinical use in the acceleration of normal bone healing. In this regard among the local factors active on bone regeneration, bone morphogenetic proteins (BMPs) have been the most extensively studied, as they are potent osteoinductive factors [8]. Additional growth factors include platelet-derived growth factor (PDGF), TGFbeta, insulin-like growth factor 1 (IGF1), vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), among others [9,10]. Extensive research is ongoing to develop formulations for minimally invasive local application, and/or novel carriers for targeted local delivery [11,12]. One current approach to enhance bone regeneration is the local application of platelet-rich plasma, which is rich in many of the aforementioned molecules [13,14]. Even if their clinical use is constantly increasing, there are several issues regarding their use, including the potential for ectopic ossification [15]. In order to mimic the endogenous growth factor production nanoparticle technology seems to be a promising approach in the future of bone regeneration [16].

While the attention was posed on local interventions inclusive of growth factors, scaffolds, mesenchymal stem cells and mechanical stimuli (the diamond concept) [17-19], the use of drugs administered systemically to promote formation and to reduce resorption in osteoporotic patients was totally overlooked for years. The fact that older age, osteoporosis and corticosteroid therapy may contribute to delayed or impaired fracture union has certainly accelerated the preclinical studies to evaluate the role of pharmacological agents in improving fracture healing [20]. If these pharmacological approaches could be translated into clinical benefit and offered to patients with osteoporosis or patients with other risks for impaired fracture healing, they could provide an important adjunct to the treatment of fractures [21]. Indeed, the use of systemic agents offers an easy, noninvasive manner to improve the healing in fractured bones.

With these premises descriptions of clinical cases treated with anti-osteoporotic drugs to ameliorate the outcome of fractures proliferated, soon followed by randomized clinical trials [22,23]. These reports were the basis for the development of consensus documents aiming to evaluate medicinal products for acceleration of fracture healing in patients with osteoporosis [24-26]. These efforts constituted the basis for the design of new clinical trials with novel compounds active on bone remodeling.

This review looks at the clinical evidence of how systemic agents influencing bone remodeling may affect bone repair and regeneration.

2. Concept of fracture healing

The most common form of bone regeneration is fracture repair that recapitulates the orchestrated steps of normal fetal skeletogenesis, encompassing intramembranous and endochondral ossification [27,28]. In normal condition, the final result is a regenerated tissue indistinguishable from the contiguous normal bone without signs of scar tissue, but with a poorly understood interindividual variability. Conversely, in certain complex clinical phenotypes bone regeneration is impaired, including large bone defects, avascular necrosis and osteoporosis.

Local interventions represent the standard of care for the orthopedic surgeon, with the final scope to increase bone formation, a process sensible to the action of number of bone cell progenitors, to their differentiation kinetics and to vascularization. However, even if widely used these strategies are associated with drawbacks and limitations to their use, to their availability, to their efficacy and cost-effectiveness.

The understanding of cellular and molecular biology of bone regeneration makes possible today to attempt targeting the cellular components relevant in the process of bone regeneration. One under-explored strategy is to target the bone regenerating niche, whose osteoblasts are indeed a key component *in vivo*. Previous experiences clearly showed that constitutive expression of the active form of the parathyroid hormone (PTH) receptor in the osteoblastic lineage led to expansion of the stem cell pool, with these effects being recapitulated through the administration of exogenous PTH [29]. These data provided evidence that the osteoblastic cells may be an attractive target for systemic pharmacological therapy aiming to improve bone repair and regeneration.

The last two decades have witnessed important discoveries in the field of agents approved for treatment of osteoporosis, developed to be administered systemically to prevent fragility fractures in low bone mass patients. Such therapeutics can act *in vivo* to stimulate endogenous cell regeneration and, being able to actively modify bone metabolism, can act *in vivo* to promote endogenous osteoblast proliferation, differentiation, and survival, and therefore fracture healing. However, no systemic treatment has yet been approved for the induction of fracture repair.

3. Fracture healing in osteoporosis

Fractures in osteoporosis greatly impair the quality of life of the affected patients. Surgical treatment is the elective intervention in some fractures (i.e., hip fractures), but a delay on fracture repair can complicate the post-surgical healing [30,31].

Osteoporosis could aggravate the problems mentioned above, as fragility fractures can be difficult to treat for the high degree of comminution, poor bone stock, compromised implant fixation, and a consequent reduction of fracture healing. However, in large trials of pharmaceutical industry for osteoporosis fracture incidence fracture healing itself is not analyzed. Several studies showed either delayed healing, no negative actions or inconsistent effects [32-37]. The controversy around the influence of osteoporosis on fracture healing exists, even though the failure rate of fixation is higher in osteoporotic bone compared to normal bone [38,39].

Although the prevention of fractures is certainly the goal in osteoporosis, a fast and uneventful healing process is certainly desirable. Despite the significant challenges presented by osteoporotic fractures, there is a paucity of clinical trials investigating the use of local or systemic factors in the management of fragility fractures [40,41]. However, a number of drugs recognized to prevent fractures in osteoporotic patients have been identified that may potentially improve fracture healing in osteoporotic patients, including bone-forming agents and antiresorptives [20,24].

4. Clinical evaluation of medicinal products for acceleration of fracture healing

In metabolic bone disorders medications are taken to directly alter bone turnover and through these actions they appear to prevent the consequences of the skeletal disease, such as fragility fractures in osteoporosis. These agents have been shown to either reduce bone remodeling or increase bone formation in order to improve bone biomechanics and decrease fracture risk. The question is: do these drugs interfere with normal bone fracture healing? Preclinical studies indicate that these agents augment fracture union, providing an important adjunct to the treatment of fractures. Conversely, little has been published on the clinical effect of these drugs in fracture healing.

In a consensus process, recommendations were offered for the clinical evaluation of potential therapies to augment fracture healing in long bone fractures. The following study objectives of a clinical study were considered appropriate: acceleration of fracture union, acceleration of return to normal function, and reduction of fracture healing complications [25]. These goals should determine subsequent study methodology and for each study design it should be stated whether reduction of a prospectively defined complication rate or acceleration of fracture healing is the primary study objective.

The guidelines should be harmonized worldwide to ensure comparability of the studies' results.

5. Drugs used in osteoporosis and fracture repair

Two classes of agents are under investigation for their effects on fracture prevention as well as fracture healing: antiresorptives and bone-forming agents (**Table 1**). The preclinical and clinical evidences of how these medicinal products influence bone healing are reviewed below.

5.1 Antiresorptive agents

Antiresorptives represent first-line treatment agents in the management of osteoporotic syndrome. These include bisphosphonates, selective estrogen receptor modulators (SERMs), estrogens, calcitonin, and RANK ligand inhibitors. The current evidence supports both the continuation of these therapies in patients who sustain fractures while receiving a medication and the initiation of these agents in patients who sustain a fragility fracture.

5.1.1 Bisphosphonates

Bisphosphonates, the most widely used agents to treat osteoporosis, are able to prevent osteoporotic fractures through the *in vivo* inhibition of bone remodeling reducing first bone resorption and subsequently bone formation. As bone remodeling is extremely relevant in fracture healing for the progression from callus formation to the organization of new bone tissue, controversies exist on the usefulness of bisphosphonates in the promotion of fracture repair. Moreover, long-term exposure to bisphosphonate therapy was recently shown to be associated with an increased risk of atypical hip fractures [42].

Basic science investigations have demonstrated that administration of bisphosphonates can actually enhance fracture repair, even though the callus volume was increased [22,23,43,44]. Clinical studies have further shown that systemic bisphosphonate therapy improves periprosthetic bone mineral density (BMD), screw fixation or bone repair [45-50].

Further research is needed to determine whether clinically significant anabolic effects of bisphosphonates can be seen using current dosing parameters.

5.1.2 Denosumab

Denosumab, the newly approved antiresorptive treatment for osteoporosis, as bisphosphonates in preclinical studies demonstrated increased callus volume and delayed remodeling, with no influence on callus mechanical properties [51]. Even though no clinical data on fracture healing in denosumab-treated patients have been published, no adverse effects were observed in fracture repair in patients treated with denosumab in osteoporosis and cancer patients.

5.1.3 Estrogen and SERMs

Currently, inhibitors of bone resorption, such as estrogen and SERMs, are effective in the treatment of osteoporosis in postmenopausal women. In preclinical studies raloxifene and estrogen significantly improve fracture healing in osteoporotic bone after osteotomy and stable internal fixation with regard to callus formation, resistance, and elasticity [52].

5.2 Bone-forming agents

As an alternative to the local augmentation of bone regeneration, the use of systemic anabolic agents is under extensive investigation. An anabolic agent is defined as an agent that

Table 1. Drugs developed or under development of the prevention of fragility fractures in osteoporotic patients.

Antiresorptives	Anabolics
Alendronate	Parathyroid hormone peptides
Bazedoxifene	Strontium ranelate
Calcitonin	Anti-sclerostin antibody
Denosumab	
Estrogen	
Ibandronate	
Raloxifene	
Risedronate	
Zoledronate	

increases bone strength by increasing bone mass as a result of an overall increase in bone remodeling combined with a positive bone balance.

5.2.1 *PTH peptides*

Current evidence suggests a positive role for PTH peptides in fracture healing. Currently, two PTH molecules, PTH 1-34 (teriparatide) and PTH 1-84, are marketed as anabolic agents in osteoporotic patients. When injected subcutaneously once a day in osteoporotic patients they increase cancellous bone formation, bone mineral density, and reduce the risk of fragility fractures [53,54].

As preclinical studies showed that intermittent PTH administration enhance bone repair [55], clinical studies were designed into their off-label use as anabolic agents in complex conditions requiring enhancement of bone repair. The only randomized, double-blind, placebo-controlled study of teriparatide in fracture healing investigated the potential for accelerated fracture healing in 102 postmenopausal women with a distal radius fracture that was treated nonoperatively [56]. Although this study did not meet its primary end point (accelerated median time for 40-µg teriparatide group compared with the placebo group), the data showed accelerated median time healing of three cortices in the 20-µg teriparatide group [56]. In a *post hoc* subgroup analysis, the data suggest that radiographic quality at an early time point might be a sensitive variable, perhaps better than time to cortical continuity [57]. These results, together with a number of anecdotal case reports [58] suggest that there may be a role for the standard 20-µg/day dose of teriparatide to assist fracture healing. This should be particularly true in the compromised cases.

Other metabolites of PTH are anabolic to the skeleton. These include the full-length molecule PTH 1-84 and the truncated portion of the active form PTH 1-31. Preclinical and clinical reports have confirmed their abilities to increase bone formation [59-61].

Since imbalanced bone turnover (excessive bone resorption and deficient bone formation) is the main reason for deteriorated fracture healing in osteoporotic patients, it is plausible that combined use of anabolics and antiresorptives may have additive effects on callus formation in osteoporotic fractures, namely to inhibit excessive bone resorption and stimulate new bone formation simultaneously. This hypothesis was proven in an experimental study in rodents, where PTH (1-34) and zoledronic acid treatment resulted in an additive effect on callus formation [62].

5.2.2 *Strontium ranelate*

Strontium, a trace element found in calcareous rocks and ocean water, is able to increase bone volume and prevent bone loss. These characteristics made strontium increasingly attractive for the prevention and treatment of osteoporosis, through its anabolic function [63]. Strontium ranelate, the marketed agent for the prevention of fragility fractures, in contrast with other anti-osteoporotic drugs, induces both antiresorptive and bone-forming effects, supporting a dissociative action on bone resorption and formation and rebalancing bone metabolism in favor of bone formation. The dual effect of strontium ranelate has the potential to positively influence bone regeneration.

Preclinical studies showed a positive effect of strontium ranelate on both osseointegration and fracture healing [64-68], with effects on callus strength superior than those of teriparatide [69]. Evidences from case reports of complicated long bone fractures also suggest that strontium ranelate accelerates fracture healing [70,71]. A positive effect of strontium ranelate on bone healing is an interesting possibility and it is, therefore, not surprising that a randomized clinical study has been recently initiated to evaluate the effect of strontium ranelate in accelerating fracture healing.

5.2.3 *DKK1 and sclerostin antibodies*

DKK1 and sclerostin, Wnt signaling proteins, are potent inhibitors of bone formation. Consequently, efforts were made to develop neutralizing antibodies, capable to increase both cortical and trabecular bone formation. Preclinical studies were designed to demonstrate the effects of these antibodies in accelerating fracture healing [72,73].

Two Phase II clinical trials with a sclerostin antibody administered to patients with acute tibial diaphyseal fractures or displaced intertrochanteric hip fractures are currently enrolling. Similar trials are in developments with DKK1 antibody treatment.

5.2.4 *Calcium-sensing receptor antagonists*

Ronacarelet is an orally active, potent and selective calcium-sensing receptor (CaSR) antagonist (calcilytic). Short-term antagonism of the CaSR in the parathyroid cell results in stimulation and release of endogenous PTH, increasing bone formation markers [74-76]. These data, together with the known effects of PTH on bone metabolism, suggest that ronacarelet may enhance distal radius fracture healing. In a recent randomized, double-blind, placebo-controlled, parallel-group, proof-of-concept study ronacarelet did not

show significant effect on duration of distal radius healing by radiograph and CT scan, time to cast removal, clinical symptoms, grip strength, or range of motion.

6. Time for pharmacological intervention

The choice of the test time to administer systemic anti-fracture therapies for improving bone healing is still a matter of investigation and controlled clinical trials need to be conducted.

In a recent report, Takahata and colleagues described the use of PTH 1-34 as an adjuvant therapy for massive allograft healing in a murine model [77]. Their results support the potential use of PTH 1-34 within an ideal treatment use after the endochondral phase to promote osteoblastogenesis and achieve union with modest callus formation.

7. Conclusions

One of the expected great advances for fracture care in orthopedics is the registration of systemic pharmacological agents that will improve the healing process in both surgical and nonsurgical fracture care. While local therapies, based on drugs, cells and scaffolds, are currently in use by orthopedic surgeons, systemic agents are not still registered with the indications "improvement of fracture healing." However, the understanding of the cellular and molecular mechanisms that underlie fracture repair and regeneration made possible for a number of medicinal agents to be recognized as potential interventions to control the different steps of the healing process. The development of guidelines for controlled clinical trials to test these hypotheses has been made available and randomized trials have been completed and are ongoing. Advances in our understanding of the role of these drugs in bone repair will allow us to use these systemic agents in a clinical setting.

8. Expert opinion

Osteoporotic bone shows a prolonged and impaired healing process compared with normal bone. The question arises as to whether substances, which are successful in the treatment of osteoporosis, are efficient in improving fracture healing in the osteoporotic bone as well.

Although an increasing number of drugs are marketed for the prevention of osteoporotic fractures, none of these systemic treatments as yet been approved for the induction of fracture healing. However, the agents approved for the treatment of osteoporosis are actively modulating bone metabolism, and may consequently influence fracture repair.

Several drugs are currently being tested for improvement of fracture repair, with two outcome variables, the time to cortical continuity and the appearance of the callus at 5 weeks. Further clinical investigations with these drugs are warranted, before they would become standard treatments in the acceleration of fracture healing.

The ongoing research to enhance bone quality by currently available products for the prevention and treatment of osteoporosis makes possible to identify new agents and to develop better delivery systems will greatly enhance the management of bone quality-related injuries and diseases in the future.

Advances in our understanding of the role of anti-osteoporotic drugs in fracture repair are already allowing us to use these systemic agents in a clinical setting.

Declaration of interest

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