Repurposing denosumab for recalcitrant bone healing

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SUMMARY

Fracture healing has four phases: haematoma formation, soft callus, hard callus and remodelling. Often, non-healing fractures have an arrest of one of these phases, which need resurgery. We have repurposed denosumab for impaired fracture healing cases to avoid surgical intervention. Here, we report a series of three cases of impaired fracture healing where denosumab was given 120 mg subcutaneous dosages for 3 months to enhance healing. All the three cases have shown complete bone union at a mean follow-up of 6.7 months (5–9 months) as assessed clinically and radiologically, and have observed no adverse effect of the therapy. Denosumab given in this dose aids fracture healing by increasing callus volume, density and bridges the fracture gap in recalcitrant fracture healing cases where the callus fails to consolidate.

BACKGROUND

Impaired healing after a fracture has been a long-standing challenge and has attracted much attention recently, with the availability of many locally implanted or injected growth factors.[1] The gold standard for treating such cases is using autologous bone grafts to enhance the bone healing process, but it has certain disadvantages of a resurgery requirement, limited graft availability and graft site morbidity. A cost-effective and attractive option would be a systemic pharmaceutical agent to achieve bone healing. Thus, there is an unmet need for medications that can stimulate fracture healing.

Denosumab has been successfully used to treat/prevent bone metastasis in metastatic cancer in 120 mg subcutaneous dosage given monthly.[1] It inhibits osteoclast activity resulting in reduced bone resorption, tumour-induced bone destruction, and increased bone formation. Denosumab in the same dosages in giant cell tumour of bone (GCTB) has resulted in cessation of osteolysis, new bone deposition, new woven bone formation and redefinition of cortical margins.[2 3]

With a similar action and dosages used in metastatic cancer and GCTB, denosumab can facilitate fracture union during the hard callus formation and remodelling phase of fracture healing. Because the fracture healing process involves the bone formation and bone resorption, it is reasonable to believe that denosumab can modulate the fracture healing process. This was seen in animal studies where denosumab altered callus' mechanical properties in healing fractures.[4 5] It increased bone mineral content and density as well as the callus volume, strength and stiffness.[4 5]

On this surmise, we have empirically used denosumab in cases with sound surgical stabilisation, including bone grafting, low callus volume could not bridge the fracture ends. Considering non-union is pathological, we have administered denosumab 120 mg monthly for 3 months.[3–5] three patients consented to a trial of this medical treatment to accentuate fracture healing.

Here, we report a series of three cases of impaired fracture healing where denosumab was administered to enhance healing. This is the only study evaluating the efficacy of denosumab in impaired fracture healing.

CASE PRESENTATION

Case 1

A 42-year-old man sustained a closed subtrochanteric fracture of the left femur following a road traffic accident. The patient was operated on elsewhere with a trochanteric locking plate and screws, which failed within 5 months of surgery. The primary surgeon revised the implant with a reversed distal femur locking plate of the right side and bone grafting. The patient presented to us at 11th postoperative month following revision surgery (figure 1). There was tenderness at the fracture site, inability to bear weight and quadriceps wasting. Radiographs showed a well-fixed implant with impaired fracture healing. There was some non-bridging callus that was present at the fracture site.

Since the implant fixation was stable and bone ends had callus, which was not abundant, it was decided that to accentuate the callus formation, denosumab would be administered. The dose used was 120 mg subcutaneous monthly for 3 months. At the end of 6 months, radiographs showed a good bridging callus around the fracture site in all four cortexes in anteroposterior and lateral views (figure 1). The patient was asymptomatic, was able to walk unaided full weight bearing on the affected extremity, and fracture site tenderness was absent. The patient was asymptomatic at the last follow-up of 39 months after starting the denosumab therapy.

Case 2

A 50-year-old man underwent humeral shaft plate fixation for mid-shaft humerus fracture (figure 2). At 9 months follow-up, X-rays did not show healing, and therefore, the patient underwent a second surgery. Replating, along with bone grafting, was done. Radiographs at 7 months after the second surgery showed callus formation but no bridging. Denosumab was given in a similar dose as given in case 1 to accentuate callus formation. X-rays at 3 months showed increased callus volume as compared with previous X-rays. At 5 months of postdenosumab therapy, the radiological union was evident on radiographs with bridging callus in both anteroposterior and lateral views. The fracture site

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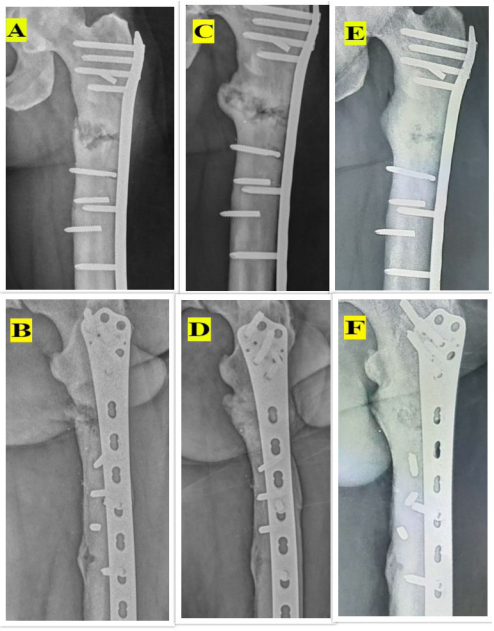

Figure 1 (A, B) Anteroposterior and lateral radiograph of a 42-year-old patient with impaired fracture healing of left subtrochanteric femur fracture inspite of two surgeries and bone grafting, (C, D) radiographs at 3 months showing bridging callus formation across the fracture ends after denosumab therapy, (E, F) radiographs at 6 months postdenosumab therapy showing complete union of the fracture.

was non-tender, and the patient was asymptomatic. The patient was asymptomatic at the last follow-up at 32 months after starting the denosumab therapy.

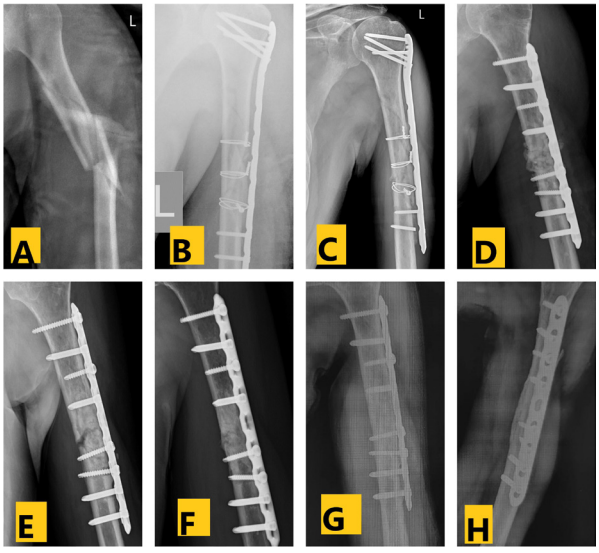

Figure 2 (A) Preoperative radiograph of a 50-year-old male patient with fracture shaft humerus, (B) postoperative radiograph showing plate fixation, (C) radiograph at 9 months showing non-union and implant failure, (D) revision surgery with bone grafting and replating was done, (E) radiographs at 7 months postrevision surgery showing impaired fracture healing when denosumab treatment was started, (F) radiographs at 3 months after starting the denosumab therapy showing obliteration of the fracture gap and callus formation, (G, H) anteroposterior and lateral radiographs at 5 months after starting the denosumab therapy showing complete union at the fracture site.

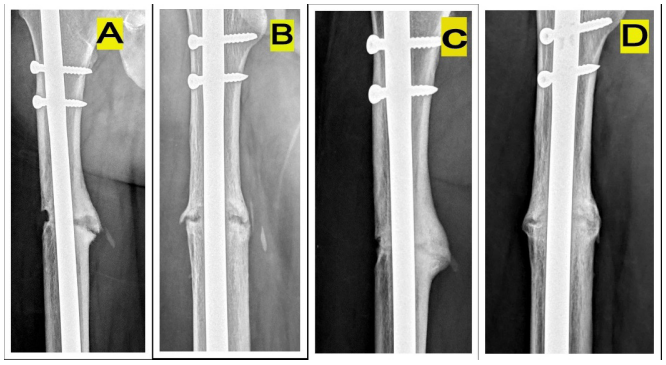

Figure 3 (A, B) Anteroposterior and lateral radiograph of a 19-year-old patient at 10 months postbone grafting procedure showing impaired fracture healing of right diaphyseal femur fracture, (C, D) radiographs at 9 months postdenosumab therapy showing complete union of the fracture.

Case 3

A 19-year-old man underwent closed intramedullary nailing for shaft femur elsewhere. Bone grafting was done at 8 months post-surgery as the fracture failed to unite (figure 3). The patient presented to us at 10 months after the bone grafting procedure with impaired fracture healing. Callus was evident but was not abundant and non-bridging. Denosumab was given in a similar dose as prescribed in previous cases to accentuate fracture healing. At 9 months of postdenosumab therapy, fracture showed complete union with bridging callus formation. The patient was asymptomatic at the last follow-up at 28 months.

OUTCOME AND FOLLOW-UP

All the three cases have shown complete bone union at a mean follow-up of 6.7 months (5–9 months) as assessed clinically and radiologically, and have observed no adverse effect of the therapy. At the last mean follow-up of 33 months (28–39 months), all the patients were asymptomatic. Side effects of denosumab include hypocalcaemia or osteonecrosis of the jaw. We did not encounter any such side effects in this series of 3 cases.

DISCUSSION

The bone healing process has four phases: haematoma formation with accompanying inflammatory phase, soft callus formation, hard callus formation and bone remodelling.[6] A haematoma is formed at the fracture site due to vessel disruption leading to the infiltration by cells of the innate immune system. They in turn recruit cells of the adaptive immunity and mesenchymal stromal cells leading to the inflammatory phase. In the soft callus stage, fibrocartilage tissue fills the fracture area and provides primary stability. Cartilaginous tissue matures, hypertrophies and starts to mineralise, leading to hard callus formation, which is made up of woven bone. In the last stage of remodelling, the woven bone is replaced by lamellar bone.

The underlying cause for the fracture non-unions or delayed unions is multifactorial. The two basic principles in treating such cases is optimal fracture stabilisation and good biology of the fractured ends. If the fracture is adequately stabilised and bone ends are still viable, then the fracture can unite.[6] If required, a fracture union can be stimulated/enhanced by some pharmaco-therapeutic agents. Biological agents like mesenchymal stromal cells, bone morphogenetic protein, vascular endothelial growth factor, platelet-rich plasma, have been tried. Clinical data supporting these biological agents' efficacy is lacking; further, the

availability and cost-related issues also pose a concern. Various osteoporotic medications have been tried to accentuate fracture healing properties, including teriparatide, bisphosphonates, strontium ranelate. Denosumab has recently been approved for use in osteoporosis, but its role in fracture healing is unknown.

Denosumab is a very potent antiresorptive drug. It is a fully recombinant monoclonal antibody that binds to the receptor-activated nuclear factor κB ligand (RANKL).[7] RANKL, which is produced by osteoblasts, is prevented from binding to the RANK receptors on osteoclasts' surface and its precursor cells by this drug. This leads to a reduction in osteoclast recruitment, formation, activity and survival, thereby inhibiting osteoclastogenesis.[8] As resorption of the calcified bone matrix is integral to bone healing, its inhibition by denosumab was thought to interfere with fracture healing also. This was, however, refuted by the FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months) trial, the largest clinical study on denosumab.[7] Based on this trial, Adami *et al* concluded that postmenopausal osteoporotic women treated with denosumab were not at risk of delayed union, even if denosumab was administered at or close to the time of fracture occurrence.[7]

Evidence of denosumab being useful for fracture healing has been shown in an animal study conducted by Gerstenfeld *et al*.[2] They studied the effects of two osteoclastic inhibitors differing in their mechanism of action viz., alendronate and denosumab on femoral fracture healing in male human RANKL knock-in mice. At both three and 7 weeks, micro-CT showed that the callus volume and bone mineral capacity were significantly greater in denosumab treated femur than both alendronate and control groups. Qualitative histology showed that both these drugs delay fracture callus remodelling. Whereas bisphosphonates inhibit only mature osteoclasts, denosumab inhibits both mature and immature osteoclasts and halts the process of osteoclastogenesis. Despite this, the callus' mechanical strength was significantly greater in both these groups compared with the controls.

Based on the review of literature and animal studies, Hegde *et al*, in their review article, concluded the following effects of denosumab on fracture callus.[9] Its antiosteoclastic properties enhance the mechanical strength of the callus by increasing callus volume and density. Denosumab delay callus remodelling thus enhances the load-carrying capacity and torsional strength of the callus.

Studies have shown the beneficial role of 120 mg subcutaneously monthly dosages of denosumab in GCTB and the management of skeletal-related bone events in metastatic cases. When given subcutaneously in 120 mg dosages over 3 months, it has caused the cessation of osteolysis, new bone formation and redefinition of ill-defined cortical margins in GCTB.[4 5] Same dosages have also been used to manage skeletal-related events in metastatic cancers.[3] Agarwala and Vijayvargiya have shown the effectiveness of denosumab in 120 mg subcutaneous dosages given for 3 months in aseptic loosening associated intrapelvic prosthetic migration.[10] This therapy was found to be effective in the cessation of osteolysis, preventing further migration of the prosthesis and stabilising the protrusio by forming new bone around the prosthesis.[10]

Our study has used 120 mg subcutaneous dosage monthly for 3 months in impaired fracture healing cases, where it has resulted in bridging callus formation and fracture union. This was very well reciprocated both clinically and radiologically, where tenderness at the fracture site disappeared. Patients became asymptomatic and could walk unaided. Radiologically, the fracture gap disappeared, and bridging callus formation was seen. Based on the review of the literature, there is enough evidence to explain the effect of denosumab in our study to enhance callus volume, density and fracture union.

This is the first reported clinical study on denosumab being used effectively for fracture healing to the best of our knowledge. All the three cases have shown complete bone union at a mean follow-up of 6.7 months (5–9 months) as assessed both clinically and radiologically, and have observed no adverse effect of the therapy. However, large case series and randomised control trials will be more useful to validate our findings.

Patient's perspective

Message from Case 1—'Stay positive and make it happen;—is the mantra I got from the Doctor and his team right from the first time I met him in the opd. I had undergone multiple surgeries under various doctors in order for my fracture to heal. I was looking for an alternative and I travelled long distance for treatment and I met Doctor here and he suggested me denosumab injection and told me it will take 6–7 months before we start seeing results and to stay positive. It exactly took 6 months for it to start healing. I sincerely thank him and his team.

Message from Case 2 patient—After my trauma I was operated for my arm fracture. My pain never decreased inspite of revision surgery and bone grafting procedures. I consulted many doctors and every one suggested other surgeries. I was mentally and emotionally disturbed and worried about my arm. In the turn of events, I met Doctor who counselled me and gave me an option of denosumab injecton. It worked wonders for me.

Learning points

- Denosumab given in 120 mg subcutaneous every month for 3 months aids fracture healing by increasing callus volume and callus density, thus bridges the fracture gap in recalcitrant fractures.
- However, it should be used as an adjuvant and not an alternative to the standard principles of fracture fixation.
- The authors believe that this is an exceptional repurposing of a medically successful principle to preclude surgical reintervention.

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