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Review

Bone fracture healing: Cell therapy in delayed unions and nonunions

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ABSTRACT

Bone fracture healing impairment related to mechanical problems has been largely corrected by advances in fracture management. Better protocols, more strict controls of time and function, and hardware and surgical technique evolution have contributed to better prognosis, even in complex fractures. However, atrophic nonunion persists in clinical cases where, for different reasons, the osteogenic capability is impaired. When this is the case, a better understanding of the basic mechanisms under bone repair and augmentation techniques may put in perspective the current possibilities and future opportunities. Among those, cell therapy particularly aims to correct this insufficient osteogenesis. However, the launching of safe and efficacious cell therapies still requires substantial amount of research, especially clinical trials. This review will envisage the current clinical trials on bone healing augmentation based on cell therapy, with the experience provided by the REBORNE Project, and the insight from investigator-driven clinical trials on advanced therapies towards the future. **This article is part of a Special Issue entitled Stem Cells and Bone.**

Contents

Introduction

Bone fracture clinical management is oriented to obtain bone healing in the shortest time frame, with the best possible functional recovery, and with less complications. However, an overall rate of 5 to 10% delayed union or nonunion is widely accepted as a perceived proportion

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for bone healing problems, although this figure is not homogenous. Rather, different nonunion rates are found in different types of fracture, somewhat ranging from up to 18.5% in the tibia diaphysis [1] to 1.7% in the femoral shaft after reamed nailing [2].

The definition of delayed union and nonunion or pseudarthrosis certainly deserves more discussion. Those cases that correspond to a different healing rate than expected (slow healing rate) should be clearly separated from those in which the bone healing is no longer expected without treatment. A better understanding of fracture healing biology would help in fostering preclinical studies and clinical proposals in both of these directions: accelerating bone fracture healing in case of slow healing rate, based on biological stimulation, and promoting bone fracture healing in case of no healing expectations, based on redeveloping the bone regeneration capability, whether fully lost or at least under the required threshold to healing.

Major limb injuries related to traffic accidents and multiple trauma are a major health issue in developed countries, resulting in long treatments with substantial socioeconomic effects. But these injuries are also severely impacting less developed countries, where secondary complications frequently generate major disabilities [3]. Long bone fractures are difficult and slow to heal and may require months until consolidation is completed. Long treatments not only associate significant loss of working days with economic effects on the patient and the society, but also carry the risk of nonunion and permanent disabilities related to malunion, joint stiffness, muscular atrophy, or reflex sympathetic dystrophy.

The ability of fractured bone to regenerate and undergo repair may be compromised when insufficient osteogenic reaction is observed in the fracture callus, up to developing an atrophic nonunion. Those cases cannot be solved through a mechanical approach, as occurs with hypertrophic nonunions. Treatment of these atrophic nonunions requires some form of bone healing augmentation, providing that vascularization is sufficient and confirming that infection is absent.

Conventional, standard treatment to augment bone healing is based on bone autograft, today's most accepted gold standard. The application of autologous cancellous and corticocancellous grafts, or larger, even vascularized, segmental bone grafts (frequently constructed out of the fibula) when the defect exceeds some centimeters, may permit the most appraised personalized management to this problem. Yet this classical orthopedic approach may be not appropriate. And this happens when the autograft strategy has already failed, when the osteogenic potential of the available donor site is altered (due to cell scarcity, fibrous tissue abundance due to previous harvesting, or other impairments), or when the risk/benefit evaluation of the autologous bone graft obtention is unbalanced or refused by the patient.

Alternatively proposed strategies include those relying on the osteoconductive or osteoinductive capabilities of an implanted tissue (such as allograft or demineralized bone matrix) or a synthetic material (such as bioceramics in different forms and compositions). Also, different strategies have been defined to supplement potential molecular deficiency in the stimulation of local cell differentiation in the osteoprogenitor line (such as BMP or other growth factor local deliveries). These strategies rely on the surrounding or available cells that might eventually produce the required local bone regeneration. The expected fracture healing is seriously constrained in cases where previous efforts to heal the fracture have failed. Particularly in those cases with a supposed cell insufficiency, cell-based alternatives developed over mesenchymal stem cells (MSCs) [4] have been proposed, and are currently under investigation and evaluation.

In this context, this review progresses from clinical concepts of bone healing impairment to advanced therapies under trial [5]. In this journey, cellular and molecular bases of bone regeneration in fracture healing will be considered as the foundations of so-called therapy platforms [6], state of the art and recent contributions to bone induction and augmentation will be appraised, and particular emphasis will be placed on cell therapy proposals and current cell therapy based orthopedic clinical trials.

Clinical bone healing impairment: from hypertrophic to atrophic nonunions

In a normal biological environment, many skeletal fractures heal uneventfully in the first 6 to 8 weeks. In case of an impaired bone healing process due to a disturbed biological or mechanical environment, or in cases where thick cortices are involved such as in femoral and tibial diaphysis, fractures may take a longer time to heal [7]. Per conventional definition, if a fracture is not healed after 4 months, it can be considered a delayed union. If no bony healing is obtained in 6 months after the fracture, it can be clinically considered as nonunion, although the diagnosis requires specific radiological features showing bone ending changes.

There are two distinct variants of nonunions with opposed underlying pathomechanisms, namely hypertrophic and atrophic nonunions. A hypertrophic nonunion presents with a large, vital callus, although inefficient to regenerate bony union. On conventional radiographs, the hypertrophic nonunion displays a large, broaden callus towards the fracture gap, with a radiolucent area instead of bone bridging. Due to its radiological features (Fig. 1), the hypertrophic nonunion is also called elephant foot nonunion [8]. Its basic problem is the mechanical disturbance of the chosen fixation technique. The most recognized

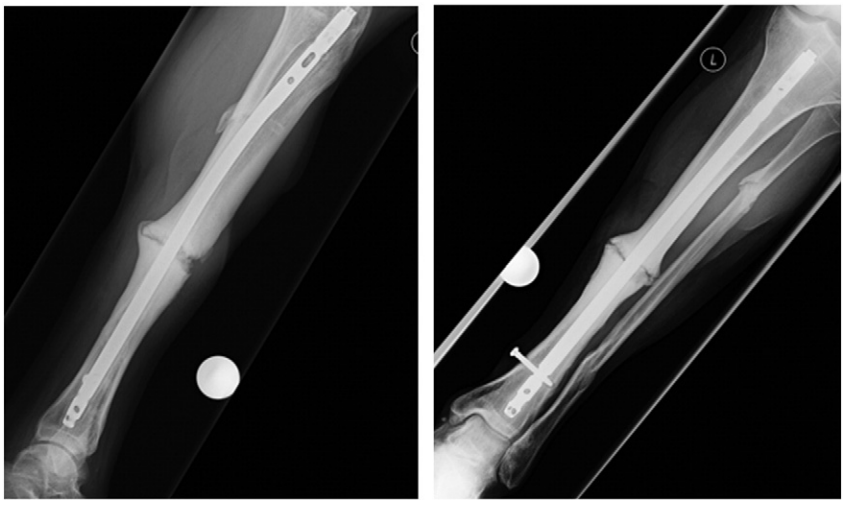

Fig. 1. Radiological AP and lateral views of a tibial midshaft hypertrophic nonunion.