



## Treatment of long bone non-unions with polytherapy: Indications and clinical results

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### ABSTRACT

The incidence of long bone non-unions has been estimated to range between 5 and 10%. Autologous bone graft usually harvested from the iliac crest continues to be the gold standard for biological enhancement of atrophic non-unions. However, its use has been hampered by minor and major donor site complications. Moreover despite possessing the properties of osteogenicity, osteoconductivity and some osteoinductivity the overall results of treatment have not been consistent with disappointing success rates at times. The concept of polytherapy for the treatment of non-unions, namely the simultaneous application of the three fundamental elements of the diamond concept, osteoprogenitor cells, growth factor and osteoconductive scaffold, appears to be an attractive alternative but more studies are desirable to validate this strategy.

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### Introduction

The vast majority of fractures progress to union<sup>78</sup> and only a small percentage of them (5–10%) are associated with impaired healing requiring further surgical intervention.<sup>9,17,79</sup>

Atrophic non-unions<sup>84</sup> are usually characterised from a deprived biological substrate and their management remains challenging.<sup>11,33,34</sup> It has been demonstrated that a stable fixation of the non-union site and a simultaneous use of autologous bone graft (ABG), facilitates fracture union with good success rates<sup>69</sup>.

Lately, with the advances made in every field of medicine, enhancement of the biology of atrophic non-unions has seen the use of alternative substances to ABG due to its limited availability and the associated donor site morbidity.<sup>1,3,5,12,15,25,50,51,74</sup> Such alternatives have been used as implantation of mesenchymal stem cells (MSCs),<sup>43,61,62</sup> growth factors (GFs) such as bone morphogenetic proteins (rhBMPs)<sup>12,21,27,37,47</sup> or autologous growth factors (AGFs) contained in Platelet Rich plasma (PRP)<sup>12,28,47,68,77</sup> and scaffolds.<sup>19,67</sup> Although it is well accepted that MSCs, growth factors and scaffolds are all essential for the evolution of bone healing according to the diamond concept,<sup>29,30</sup> clinicians have adopted the use of only one of the above options for biological enhancement at the non-union site. This strategy, otherwise known as ‘monotherapy’, has not produced consistent findings and

it is of note that in over half of the reported cases ABG has been used with disappointing results.<sup>35,55,65,88</sup>

Polytherapy can be considered as a new strategy of biological stimulation where impaired bone healing is anticipated or it is already established. This strategy would involve the utilisation and simultaneous implantation of all three fundamental components of the diamond concept: MSCs, growth factor and scaffold, assuming that a correct fixation and mechanical stability has been adequately provided.<sup>30,82</sup>

The aim of this article is to determine the evidence supporting the direct role of MSCs, Growth Factors and scaffolds in the biological enhancement of non-unions and to examine any existing evidence supporting the polytherapy approach.

### Materials and methods

Using the PubMed search engine a research of the published series on polytherapy in long bone non-unions was performed at the 10th of August 2010. The following keywords were used: “polytherapy”; OR “poly therapy”; OR “BMPs”; OR “MSCs”; AND “PRP”; OR “long bone non-unions”; OR “multi-approach”; OR “ABG”; OR “Growth Factors”. The exclusion criteria were: case reports or referring to children (age <16 years); editorials; letters; review studies and articles in languages other than English.

Data from the accumulated manuscripts were collected mainly addressing the issues of principles/stages of management of long bone non-unions, clinical and radiographic outcome and complication rates. When possible, descriptive statistical means were used to comprehensively present the reviewed evidence.

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## Results

From a considerable number of initially retrieved abstracts on polytherapy, 903 in total, based on the definition of polytherapy as simultaneous application of all three fundamental components of the diamond concept and based on the inclusion/exclusion criteria previously described, ten studies were found eligible to be included in this study.<sup>6,7,28,31,40,44,47,71,76,88</sup>

In a *vitro* study the VEGF application with MSCs showed to enhance the osteogenesis process. Moreover, the addition of recombinant human bone morphogenetic protein-2 (rhBMP-2) greatly increased osteocalcin (OC) release from MSCs promoting the healing response.<sup>44</sup>

Another recent study has illustrated the beneficial effect of bone morphogenetic proteins on the chondrogenic and osteogenic differentiation of human bone marrow mesenchymal stem cells.<sup>71</sup>

In two animal studies<sup>6,7</sup>, the new bone formation in femoral defects of rats was clearly superior in the group treated with the combination of human-MSCs (hMSCs) and rhBMP-7 compared to rats treated with rhBMP-7 or hMSCs alone. The high bone apposition was demonstrated by radiographic analysis and histological examination.

In a dog study, the simultaneous application of rhBMP-7 and MSCs increased the local population of cells and the connective tissue progenitors in a canine femur defect model.<sup>76</sup>

The association of autologous growth factors (AGFs), contained in platelet rich plasma (PRP), and autologous bone graft (ABG) in a tibial critical size defects of the 16 mini-pigs, was compared with application of autologous cancellous bone graft alone.<sup>40</sup> The histomorphometrical analysis revealed that the area of new bone formation was significantly higher in the ABG-PRP group. Nevertheless the use of platelet-rich plasma (PRP) to improve the bone defect healing is discussed controversially. In a dog model of mandibular defects, the association with PRP and ABG did not prove to be beneficial.<sup>28</sup>

In a multicenter study<sup>48</sup> of 30 cases of femoral non-unions, healing in 26 out of 30 cases operated with rhBMP-7 was observed. In a subgroup of this study, 12 cases were treated with a combination of ABG and rhBMP-7 and union was successful in 10/12 patients (83.3%). One of these two failures had undergone four previous procedures without success.

Zimmerman et al.<sup>88</sup> reported on 26 long bone non-unions of the tibia shaft treated with rhBMP-7. Union was observed in 24/26 (92%) cases, but after profound analysis of subgroups of this series, it was noted that 8 cases were operated with the simultaneous application of rhBMP-7+ABG and 18 cases with rhBMP-7 alone with or without revision of the osteosynthesis. The union rate in the group treated only with rhBMP-7 was 88.8% (16/18 cases), whereas in the group of combined implantation of ABG and rhBMP-7 it reached 100%.

Finally, in another clinical series, the simultaneous implantation of ABG and rhBMP-7 in 45 long bone non-unions was associated with a success rate of 100% with a median time of clinical and radiographic union of 5 and 6 months respectively.<sup>31</sup>

## Discussion

ABG possess all the three desirable properties that a graft material should retain being osteogenicity, osteoinductivity and osteoconductivity. However, from the practical point of view, prior to the implantation, there is no testing of the autologous graft to investigate whether it does possess all these properties. It is possible that variations that exist from host to host in terms of the presence and the extent of these biological properties could provide a reasonable explanation of the failure rate of cases where the ABG has been used alone as the primary biological stimulus in

patients with fracture non-unions. Failure rates have been reported as high as 50%.<sup>49</sup> Moreover the harvesting and handling process prior to the implantation could affect the effectiveness of ABG. The reported healing rates where ABG has been used as a biological stimulant for the treatment of long bone non-unions range from 60% to 100%.<sup>26,27,49,53,88</sup> Additionally, there is universal agreement amongst clinicians that the harvesting process is associated with prolongation of surgery and an incidence of chronic morbidity not to be underestimated.<sup>36,39,69,72,87</sup> Moreover, the cost of harvesting can be as high as the cost of implanting a growth factor and it has been argued by some authors that the prolonged surgery time can lead to a proportional increased risk of infection.<sup>36,39</sup> These limitations of ABG have stimulated clinicians to apply other biological enhancement options for the treatment of non-unions. But even these alternative strategies have not shown consistently favourable results.<sup>2,12,16,19,20,22,24,27,35,43,47,48,56,62,65,88</sup>

Overall, for the treatment of long bone non-unions based on the concept of monotherapy such materials have been used as:

- Allografts, xenografts or synthetic bone substitutes (HA, TCP, BCP) exhibiting osteoconductive properties. However, such materials require prolonged periods for reabsorption, pose inadequacy for filling successfully large bone gaps and containment can be difficult. Therefore, they are not ideal when used alone for the treatment of atrophic long bone non-unions.<sup>19</sup>
- Demineralized bone matrix (DBM) obtained by demineralization of cortical bone. It has osteoinductive properties due to the presence of "bone morphogenetic proteins" and other factors such as transforming growth factor beta (TGF- $\beta$ ) and insulin-like growth factor (IGF).<sup>24</sup> However, DBM has demonstrated a less osteoinductive capacity compared to ABG<sup>22</sup> and has shown a high questionable variability of concentration of BMP-2 and BMP-7 in some products.<sup>2</sup>
- MSCs. Studies based on cell therapies have focused on the implantation of concentrated bone marrow aspirate.<sup>43,62,75</sup> In addition to their pluripotent properties of plasticity, MSCs are considered osteogenic progenitor cells with demonstrated ability to repair bone defects.<sup>16,57,61</sup> However, one aspect that should not be underestimated is the very low concentration of MSCs in the bone marrow tissue.<sup>16,41,42,58,59,60,70</sup>
- Autologous growth factors (AGFs) are contained in PRP (platelet rich plasma) obtained by concentration of autologous platelets. It is an advanced product of Blood Management, a biologically active concentrate of mediators extracted from the patient's plasma that seems to accelerate the normal and physiological healing processes of bone, cartilage and soft tissue.<sup>54</sup> It has a similar but much stronger effect as a haematoma, thanks to the high concentration of thrombocytes. Various cytokines (PDGF, TGF $\beta$ 1- $\beta$ 2, IGF1-2, VEGF) with a chemotactic, mitogenetic and angiogenetic properties are delivered by degranulation of activated platelets.<sup>52</sup> However, recently discouraging results have been reported.<sup>13,64,85</sup> A randomized study comparing the use of PRP to rhBMP-7 for the treatment of 60 long bone non-unions showed inferior results in the group of patients treated with PRP.<sup>12</sup> In conclusion, the AGFs contained in PRP, as clarified by preclinical and clinical data, are: (i) promoters to cellular division (mitogenesis), (ii) not specific for the bone cells, (iii) unable to promote the differentiation of mesenchymal cells and to induce new bone formation<sup>52</sup>. Hence, their implantation for the treatment of long bone non-unions should be exercised with caution.<sup>12,13,85</sup>
- Synthetic growth factors (BMPs). BMPs pose the property of osteoinduction being defined as the phenomenon in which perivascular mesenchymal stem cells are transformed into osteoprogenitor cells capable of forming new bone.<sup>14,52,86</sup>

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