JCP digest
Issue number 92 (2021:8)

EFP 30 years (1991-2021) promoting periodontal health for a better life
European Federation of Periodontology

Summarised from *Journal of Clinical Periodontology*, Volume 48, issue 8 (August 2021), 1111-1125

Editors: Phoebus Madianos & Andreas Stavropoulos, EFP scientific affairs committee

Rapporteurs:
María Vilar Doceda, Pierre-Yves Gegout, Marianna Gavriiloglou, Elizabeth Ibrahim, and Alexia Larderet with Dr Catherine Petit and Prof Olivier Huck

Affiliation:
Postgraduate programme in Periodontology and Implant Dentistry, Dental Faculty, University of Strasbourg, France

study

Using a tissue-engineered biocomplex for periodontal reconstruction

Authors:
Danae A. Apatzidou, Athina A. Bakopoulou, Kokkona Kouzi-Koliakou, Vassilis Karagiannis, Antonis Konstantinidis

Background

Various innovative biomaterials, bioactive agents, and flap designs have been proposed to enhance periodontal healing. However, their clinical outcomes remain unclear. To obtain convincing results, established protocols for their application, appropriate dosage, and therapeutic indications are required.

At present, therapies based on mesenchymal stem cells (MSCs) therapies are being developed as a safe and predictable way to reconstruct intrabony defects. MSCs can be increased *ex vivo* from a small tissue biopsy or they can be minimally manipulated in the form of micrografts. In addition, autologous alveolar bone-marrow MSCs (a-BMMSCs) have been commonly used and have proved to be the most suitable cell source for the intended clinical application.

To guide tissue regeneration, collagen scaffolds play a central role allowing the adhesion, proliferation, and differentiation of stem cells. In addition, platelet concentrates provide a source of growth factors that can boost tissue regeneration.

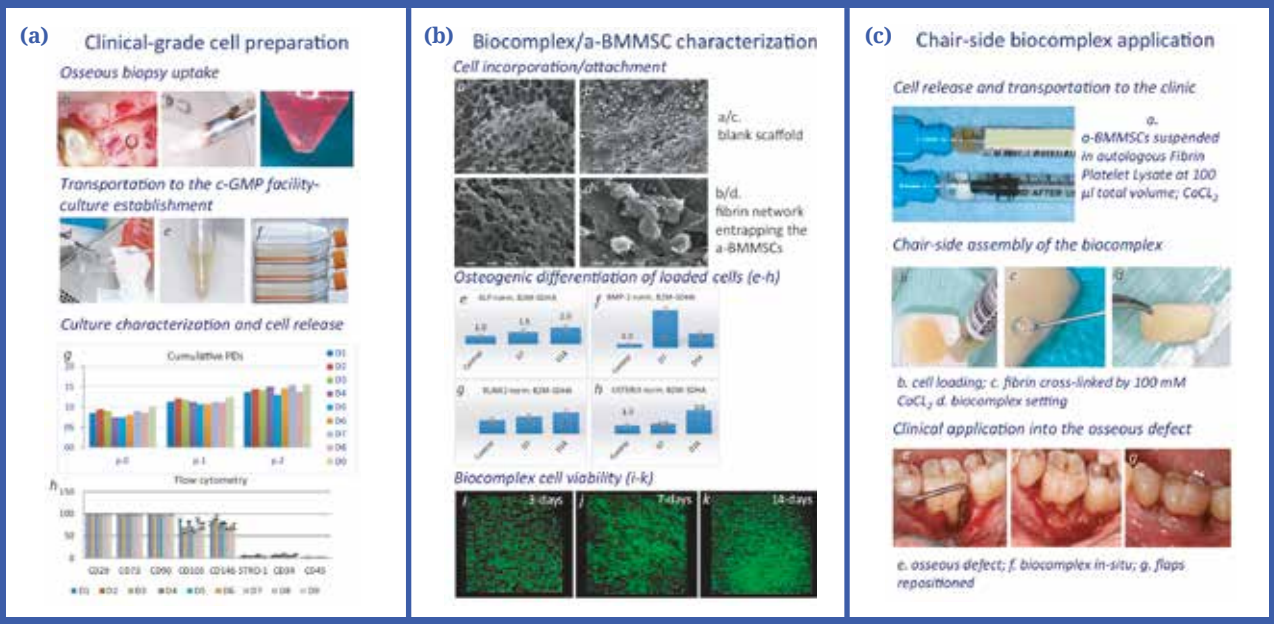
Aim

This study proposed an alternative therapeutic strategy for the regeneration of intrabony defects, using autologous bone marrow mesenchymatous stem cells (a-BMMSC) and autologous fibrin/platelet lysate (aFPL), incorporated in a collagen fleece/scaffold. The aim of this study was to evaluate the clinical efficacy and potential side effects of this therapeutic strategy.

Materials & methods

- This prospective, controlled clinical trial enrolled 27 patients diagnosed with advanced periodontitis, having at least one intrabony defect with probing pocket depth (PPD) and clinical attachment level (CAL) ≥6mm and an intrabony component ≥3mm with no radiographic evidence of endodontic/furcation involvement that required surgical intervention.
- Patients with concurrent illness or treatment compromising wound healing, alcohol intake, pregnancy/lactation, poor compliance, and full-mouth plaque index (PI) >30% were excluded from this study.
- Patients were randomly assigned to one of three groups:
  - Group A: minimal access flap with a-BMMSC (collected from the patient in an osseus biopsy and grown in culture) and an aFLP transplantation incorporated into a collagen scaffold.
  - Group B: minimal access flap with a collagen fleece enriched with aFPL but without a-BMMSC.
  - Group C: minimal access flap only.
- All subjects received oral-hygiene instructions and non-surgical periodontal treatment.
- Periodontal recordings were assessed after the non-surgical periodontal therapy and before the surgical approach (baseline), and at six, nine, and 12 months. Radiographic outcomes were evaluated at six weeks and at three, six, nine, and 12 months.
- Strict post-operative plaque control and oral-hygiene instructions were performed from one week to 12 months.
- The primary outcome of this study was the CAL gain, with recession measurements as the secondary outcome. Univariate analysis of variance with a split-plot design technique was used for clinical and radiographic variables. Pair-wise comparisons with Bonferroni adjustment compared the mean differences across groups. Subgroup analysis for smoking was conducted by two-way ANOVA before/after treatment.

Figure: Step-by-step process of the pre-clinical study methodology of the tissue-engineered biocomplex



(a) Clinical-grade cell preparation. (b) Biocomplex preparation and further ex vivo characterisation. (c) Chair-side assembly and application of the biocomplex into the osseous defect.

Results

- A total of 9/10 biopsies in group A passed the quality controls assessing possible culture infection and immunophenotypic analysis for specific surface antigen expression, as well as the growth rate and viability of the seeded a-BMMSCs.
- No adverse healing events were reported during the 12-month study period and during the three additional years following study completion.
- Clinical outcomes:
  - A significant amelioration was measured from baseline to 12 months. For all groups, the estimated marginal mean for CAL gain was 3.0mm (95% CI: 1.9-4.1mm); PPD reduction was 3.7mm (2.7-4.8mm), and the recession increment was 0.7mm (0.2-1.3mm).
  - There were no significant differences between the groups. Throughout the study, clinical parameters were continuously improved. No significant interaction effect was found between groups and time.
  - PPD closure (≤4mm) and CAL gain (≥3mm) were obtained in 55.6% of defects in group A and 50% of defects in groups B and C. During the study period, PI was maintained at a low level and bleeding on probing (BOP) was reduced.
- Radiographic outcomes: at 12 months, group B showed less reduction of the distance between the cementoenamel junction and the bottom of the defect (CEJ-BD) than groups A and C. The estimated marginal mean (95% CI) reduction was 1.8mm (95% CI: 1.4-2.2mm), 0.3mm (0-0.7mm), and 1.4mm (1.0-1.8mm) for groups A, B, and C respectively.
- Smokers were 66.6% (6/9), 50.0% (5/10), and 62.5% (5/8) in groups A, B, and C, respectively. There were no significant differences between smokers and non-smokers in either clinical or radiographic outcomes for all the treatments.

Limitations

- The sample size was small (27 sites). The sample-size calculation was estimated at 22 in each group to detect a true difference in CAL of at least 1mm.
- The inclusion of smoker patients and the wide range of tobacco consumption (4-30 packs/year) between the groups may lead to arbitrary results.
- The heterogeneity of the distribution of the intrabony defects among the groups could influence the bone-fill outcomes.
- The bone-fill calculation using 2D measurements may produce inaccurate results because of the overlapping of bone walls.
- There are no data regarding the position of the intrabony defects (molar/incisor).

Conclusions & impact

- This tissue-engineered biocomplex required three weeks of laboratory preparation after 20 minutes of surgery to obtain the biopsy from the patient. It was well-tolerated and had the advantage of fitting into any type of bone defect.
- This promising new bioengineered tool may be able to promote healing, probably because of the modulation of local inflammation and the stimulation of the local-host cells. Other therapies, based on the use of isolated cellular components (growth factors, proteins, exosomes, extra-cellular vesicles…) are expected to be an alternative to stem cells.
- Nevertheless, this study presents some disadvantages directly linked to the technique, such as cost, logistics, and preparation time.
- Future studies should consider an increase of the sample size and study period, as well as the use of more complex anatomical bone defects (two-wall intrabony defects) to obtain more accurate results.

JCP Digest issue 92, published in September 2021, is a summary of 'A tissue-engineered biocomplex for periodontal reconstruction. A proof-of-principle randomized clinical study.' *J Clin Periodontol.* 2021; 48 (8): 1111-1125. DOI: 10.1111/jcpe13464

https://www.onlinelibrary.wiley.com/doi/10.1111/jcpe.13474

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