A Health Technology Assessment Report on Role of Platelet derived Growth Factor in Intra-Osseous Periodontal Regeneration

by

Mohammad Ahmad Javaid\textsuperscript{a}

with the expert assistance of

Shahrokh Esfandiari\textsuperscript{b}

April 2013

Report No: S2013.01

\textsuperscript{a} Masters candidate, Faculty of Dentistry, McGill University, Montreal, Canada

\textsuperscript{b} Associate Professor, Division of Oral Health and Society, Faculty of Dentistry, McGill University

For more information contact Dr. Shahrokh Esfandiari at shahrokh.esfandiari@mail.mcgill.ca
The views expressed in this report are those of the author(s) and do not necessarily reflect the views of the Faculty of Dentistry, McGill University. This report was developed for the course ‘DENT 655- Health Technology Assessment’ and assumes a call from general dentists to assist decision-making in dental offices, clinical and hospitals. All are welcome to make use of it. However, to help us estimate the impact, it would be deeply appreciated if users could inform us whether it has influenced policy decisions in any way.

ACKNOWLEDGEMENTS

We wish to express our sincere appreciation to the invaluable help of the following individuals:

Martin Morris- Liaison Librarian, Life Sciences Library McGill University

Vanita Krishnan- MSc Candidate, McGill University

Kelvin Afrashtehfar- MSc Candidate, McGill University

Zeeshan Sheikh- PhD Candidate, McGill University

Mohamed Nur- PhD Student, McGill University

Hazem Eimar- PhD Candidate, McGill University

Akanksha Srivastava- MSc Candidate, McGill University
# TABLE OF CONTENTS

Executive Summary ........................................................................................................ 4

Background .................................................................................................................... 8

Rationale and Objectives .............................................................................................. 11

Material and Methods ................................................................................................ 11

Discussion .................................................................................................................... 16

References .................................................................................................................... 28
**Executive Summary**

**Background**

Restoration of lost tissue through application of principles of tissue engineering is a complex process that involves intricate interaction between cells, growth factors and scaffold. A challenge in the field of Periodontology is the regeneration of lost periodontium that includes the alveolar bone. Use of tissue engineering was actualized in the field of periodontology by introduction of Guided Tissue Regeneration. The advent of an array of new technologies together with the advances in the field of tissue engineering has helped scientists develop various biological approaches for potential regeneration of lost periodontium. These approaches include mediators of bone grafts, extracellular matrix proteins and growth factors. Platelet derived growth factors (PDGF) are a family of growth factors that have been studied most extensively in context of periodontal regeneration. PDGF is a protein that is found throughout the bone matrix. It has been demonstrated that PDGF-BB stimulation can induce proliferation and migration of osteoblasts. Promising results both in preclinical studies and clinical trials have lead to FDA approval of rhPDGF-BB for treatment of periodontal osseous defects.

**Rationale and Objectives**

The aim of the current report is to carry out a systematic review and prepare an HTA report on Role of Platelet derived Growth Factor in Intra-Osseous Periodontal Regeneration while assessing all the pertinent attributes of the given technology.

**Materials and Methods**

**Eligibility Criteria**
All human studies published in English language with a minimum follow up period of 3 months with clinical and or radiological evidence of at least 20% new bone formation were included. Abstracts without full articles were excluded.

**Search Strategies**

We performed a systematic search exploring the PubMed, PubMed Health, MEDLINE, Health Technology Assessment international, Google Scholar and Cochrane databases for articles addressing the Role of PDGF in Intra-Osseous Periodontal Regeneration. Databases were searched from Jan 1996 up to Jan 2013.

After acquisition of the abstracts, the articles were screened by the authors and checked for agreement. From the selected articles, relevant information about study design, study population, effectiveness and safety was extracted. Finally we also estimated the unit cost of rhPDGF-BB based on additional percentage new bone formed in intra-osseous periodontal defects when rhPDGF-BB was used in conjunction with scaffold material.

**Results**

A total of 57 articles were identified in systematic electronic search. After assessment by two independent reviewers, full text of 21 articles was obtained. Of the selected 21 articles, 16 papers reported clinical, radiological and/or histological evidence of new bone formation (Table 1) of which 9 met the inclusion criteria (Table 2). Out of the 16 articles that reported scientific evidence of new bone formation, 13 studies also assessed and reported the safety of use of rhPDGF-BB in human subjects (Table 3). Lastly, 3 articles of the original 16 that reported evidence of new bone formation were used to estimate unit cost of rhPDGF-BB (Table 4).
**Effectiveness**

We found 16 articles that reported clinical, radiological and/or histological evidence of new bone formation including 3 randomized clinical trials. Out of these, nine studies fulfilled the eligibility criteria. All the 9 studies reported a significant increase in percentage new bone formed when rhPDGF-BB was used in conjunction with scaffold material. Interestingly in the two clinical trials in which test sites were treated with rhPDGF plus scaffold material in comparison to control sites which were treated with scaffold material alone, percentage new bone formed was significantly more at the test sites. The mean increase in percentage new bone formed (additional bone) at test sites compared to control sites was reported to be 39% in first clinical trial conducted in 2005 and 18.1% in the second clinical trial conducted in 2011. These clinical trials were conducted in US and India respectively.

**Safety**

Thirteen studies evaluated the safety of use of rhPDGF in human subjects. Interestingly no study reported any serious adverse effects or complications in subjects treated with rhPDGF.

**Cost Analysis**

Of the original sixteen studies which reported scientific evidence of new bone formation, three studies including two multi centred clinical trials compared scaffold material and rhPDGF-BB with scaffold material alone, allowing a direct measure of additional beneficial effect (percentage new bone formed) produced by use of rhPDGF-BB. The estimated cost of rhPDGF-BB kit, which contains rhPDGF-BB and beta tricalcium phosphate (as scaffold material) is $189. In comparison, if b-TCP is used as standalone treatment modality, it costs between US $ 63 to 73.6. The kit incurs an added cost of US $ 120 TO 130 but this additional cost also results in
additional 18.1% to 39% new bone formation. There is no additional indirect cost associated with this health technology.

Legal

As per the results of our systematic search we found no relevance of Role of Platelet derived Growth Factor in Periodontal Intra-Osseous Regeneration with any ethical or legal predicament.

Discussion

The present Health Technology Assessment Report assessed the Role of Platelet derived Growth Factor in Intra-Osseous Periodontal Regeneration. All the 9 articles that met the eligibility criteria reported significant bone formation when rhPDGF-BB was used in conjunction with scaffold material. However, this significant difference in new bone formed due to use of rhPDGF-BB may not guarantee a significant improvement in clinical parameters as we could not find any evidence in the literature to support that an increase in percentage additional new bone formed by an adjunct treatment such as rhPDGF-BB results in gain in clinical attachment, reduction in mobility, improvement in gingival recession or reduction in bleeding on probing. Moreover, rhPDGF-BB incurs an additional cost of more than $100. Taken together our findings suggest that although this is a very promising technology but it may not be routinely used by an overwhelming majority of dentist until long term clinical trials prove significant improvement in clinical parameters associated with use of rhPDGF-BB.

Background
Regeneration of lost tissue using principles of tissue engineering is a complex process that requires intricate interactions between cells, growth factors and scaffold material commonly serving as the extracellular matrix [1-4]. A challenging issue in the field of Periodontology and Implantology is regeneration of lost periodontium that includes alveolar bone. In the field of Periodontology, the potential use and application of tissue engineering was first actualized with introduction of Guided Tissue Regeneration (GTR). GTR is a mechanical approach involving the use of resorbable barrier membrane which induces selective colonization of the initial defect by Periodontal Ligament (PDL) cells with subsequent regeneration of the lost tissue architecture [1]. The same principles were later used in the field of Implantology for restoration of lost bone at the planned implant site to optimize the clinical outcomes and ensure successful osseointegration [1]. Since then, advent of an array of new technologies and advances in the field of tissue engineering have lead to development of various biological approaches for regeneration of lost periodontal tissue including use of mediators of bone grafts, extracellular matrix proteins and growth factors (GFs) [1].

GFs are proteins that play a pivotal role in regulation of cellular events involved in wound healing and tissue regeneration. They bind to complementary cell surface receptors leading to intracellular signalling which then results in activation of specific genes which may subsequently alter the cellular activity and/or cellular phenotype. A number of studies have revealed that GFs can potentially enhance the tissue regeneration by various processes including cellular differentiation and proliferation [1, 5, 6][Figure 1]. But, not all the GFs have the same effect on tissue regeneration. In fact their impact is greatly affected by the binding proteins and enzymes involved in the cascade of events leading to final regeneration of the lost tissue [1].
Structure, Types and Biology of Platelet derived Growth Factor

Within GFs, the family of proteins studied most extensively, especially in context of periodontal regeneration is Platelet derived Growth Factor (PDGF) [1, 7-10]. Since the first in vivo demonstration of periodontal regeneration by PDGF in the late 1980s, more than 100 papers have been published on the positive effect of PDGF on periodontal ligament, alveolar bone cells and regeneration of periodontium [11]. PDGF is a wound healing GF which is produced naturally at the site of tissue injuries including bone fracture sites [11-13]. Animal studies involving knock out models have shown that deletion of PDGF receptor gene leads to gross anomalies in skeletal development during embryogenesis, highlighting critical importance of PDGF in development of bones [11, 14] and hence it is no surprise that it is the most thoroughly studied GF in the field of Periodontology especially for treatment of bony defects [15, 16].
PDGF is a protein that is found abundantly throughout the bone matrix. It exists as a dimer of polypeptide chains A, B and C, which are linked to one another by disulphide bonds. Five isomeric forms namely, PDGF-AA, PDGF-AB, PDGF-BB, PDGF-CC and PDGF-DD have been identified so far [17-20]. Depending on the isomeric form, PDGF molecules bind to two structurally similar but distinct receptors. The PDGF alpha receptors also known as the A-type receptors have high affinity for three isoforms [1, 21] where as beta receptors bind to PDGF-BB [21] and PDGF-DD [22] with high affinity. Studies have revealed that PDGF receptor signalling plays a pivotal role in regulation, proliferation and migration of different cells including fibroblasts and osteoblasts [23-28]. Although a study by Nister et al. [1], demonstrated that PDGF-AA does not have any chemotactic effect on human fibroblasts, recent studies have revealed that PDGF-BB stimulation leads to proliferation and chemotactic migration of osteoblasts and fibroblasts [1]. Advent of recombinant DNA technology has helped in development of recombinant human (rh) form of various GFs including all isoforms of PDGF [29-34], which are now commercially available.

Following an initial multi centred randomized human clinical trial that demonstrated that rhPDGF-BB together with insulin like growth factor (rh IGF-1) can lead to a significant bone fill in comparison to open flap debridement and placebo [35], many studies including randomized clinical trials have been conducted to test the effectiveness and safety of rhPDGF in human subjects [11, 36-50]. The promising results shown in these trials have lead to FDA approval of rhPDGF-BB for treatment of periodontal osseous defects [51].

For application in intra-osseous periodontal defects, rhPDGF-BB is used as an adjunct to scaffold material which is soaked in rhPDGF-BB instead of normal saline or patient’s own blood and hence does not incorporate any additional steps in surgical procedure. Briefly, the procedure
involves reflection of full thickness mucoperiosteal flap. This is followed by scaling, root planning and debridement. The scaffold material is then placed in a dappen dish containing rhPDGF-BB and allowed to sit for 10 minutes which results in saturation of the scaffold material with rhPDGF-BB. Once the material achieves wet sand consistency, it is gradually packed in the defect. Following the filling of the defect with rhPDGF-BB saturated scaffold material, flap is repositioned and sutures are placed.

**Rationale and Objectives**

The aim of the current report is to carry out a systematic review and prepare an HTA report on Role of Platelet derived Growth Factor in Intra-Osseous Periodontal Regeneration while assessing all the pertinent attributes of the given technology. In this report we will consider the clinical application of PDGF in context of intra-osseous periodontal regeneration and provide an update for the findings of recent clinical studies.

**Materials and Methods**

**Eligibility Criteria**

All human studies published in English language with a minimum follow up period of 3 months with clinical and or radiological evidence of at least 20% new bone formation were included. Abstracts without full articles were excluded.

**Search Strategies**

We performed a systematic search exploring the PubMed, PubMed Health, MEDLINE, Health Technology Assessment international, Google Scholar and Cochrane databases for articles addressing the Role of PDGF in Intra-Osseous Periodontal Regeneration. Databases were
searched from **Jan 1996** up to **Jan 2013** using the following keywords and search terms in various combinations; “Bone Regeneration”, “Guided Tissue Regeneration”, “Periodontal Diseases”, “Periodontium”, “Periodontics”, “Guided Tissue Regeneration”, “Periodontal”, “Periodont”, “Intraosseous”, “Intra-osseous”, “Platelet Derived Growth Factor” and “PDGF”.

Following acquisition of the titles and the abstracts, the articles were screened by the authors and checked for agreement. Judged by title and abstract, the relevant articles were read independently and evaluated against the eligibility criteria using Methodological Index for Non-Randomized Studies (MINORS) and Critical Appraisal Skills Programme (CASP) grid for randomized control trials.

From the selected articles, information about study design, study population, effectiveness and safety was extracted and summarized in Tables 1-3. Finally we also estimated per unit cost of rhPDGF-BB based on additional percentage new bone formed in intra-osseous periodontal defects when rhPDGF-BB was used in conjunction with scaffold material. Figure 2 gives an overview of the systematic search.

**Figure 2: Flow Chart of Search Strategy**
Results

A total of 57 articles were identified in the five systematic electronic searches using the keywords and search terms described previously. Following assessment by two independent reviewers (M.J and V.K), full text of 21 articles was obtained. Of the selected 21 articles, sixteen articles reported (Table 1) clinical, radiological and/or histological evidence of new bone formation, 9 of which met our eligibility criteria (Table 2). Out of the 16 articles that reported scientific evidence of new bone formation, 13 studies also assessed and reported the safety of use of rhPDGF-BB in human subjects (Table 3). Finally 3 articles of the original 16 that reported evidence of new bone formation were used to estimate the unit cost of rhPDGF-BB (Table 4).

Effectiveness

We found 16 articles that reported clinical, radiological and/or histological evidence of new bone formation including 3 randomized clinical trials. Findings of all the 16 studies are summarised in Table 1. Out of these, nine studies fulfilled the eligibility criteria and followed up the subjects for at least 3 months and reported minimum of 20% new bone formation (Table 2). Two approaches were used to calculate the percentage new bone formed: a) a surgical re-entry was performed at the end of follow up period and direct measurement was made to determine linear bone growth or b) radiographs taken at the end of the follow up period were digitalized and linear bone growth was measured which was then used to measure percentage new bone formed according to the following formula:

1 Mohammad Ahmad Javaid and Vanita Krishnan
**Linear Bone Growth (LBG)** = Cementoenamel Junction (CEJ) to base of defect at baseline - CEJ to base of defect at the end of follow up period

\[
\text{Percentage New Bone Formed} = \frac{100 \times \text{LBG}}{\text{Depth of defect at the baseline}}
\]

All the 9 studies reported significant percentage new bone formed when rhPDGF-BB was used in conjunction with scaffold material (Table 2). Interestingly in the two clinical trials in which test sites were treated with rhPDGF with scaffold material in comparison to control sites which were treated with scaffold material alone, percentage new bone formed was significantly more. The mean increase in percentage new bone formed at test sites compared to control sites was reported to be 39% in first clinical trial conducted in 2005 and 18.1% in the second clinical trial conducted in 2011 (Table 2). These clinical trials were conducted in U.S. and India respectively. The authors of the second clinical trial suggested that this marked difference in percentage new bone formed with use of rhPDGF-BB in their study in comparison to the first clinical trial could be due to the difference in mean age of patients in two trials as majority of the patients who participated in their study were in the age group that falls under the category of aggressive periodontitis. They further suggested that assortment of ethnic groups in the first clinical trial conducted in U.S. compared to cohesive group of Indians in their study lead to a basic departure from the first clinical trial [46].

**Safety**

Thirteen studies evaluated the safety of use of rhPDGF in human subjects (Table 3). Interestingly no study reported any serious adverse effects or complications in subjects treated with rhPDGF and there was no statistical difference in the reported adverse effects in study groups treated with or without rhPDGF. In fact the only reported adverse effects included mild pain and
inflammation which are expected outcomes of any surgical procedure and were treated through prescription of analgesics used in routine clinical practice.

Cost Analysis

Of the original sixteen studies which reported scientific evidence of new bone formation, 3 studies including two multi centred clinical trials compared scaffold material alone with scaffold material plus rhPDGF-BB, allowing a direct measure of additional beneficial effect (percentage new bone formed) produced by use of rhPDGF-BB [Table 4]. We have based our unit cost estimation on these two clinical trials due three reasons; firstly they carry highest weight in clinical studies in hierarchy of evidence for clinical intervention, secondly the number of patients in these two studies is significantly more than combined number of patients in all the remaining studies and lastly, both clinical trials compared beta tricalcium phosphate (b-TCP) as scaffold material alone against b-TCP with rhPDGF-BB eliminating potential confounding effect due to scaffold material in the final outcome (additional percentage new bone formed through use of rhPDGF-BB).

In the clinical trial conducted by Jayakumar et al., the scaffold material and rhPDGF-BB was provided by Virchow Biotech Private Limited, Hyderabad, India. Despite our efforts, the company did not disclose the cost of their rhPDGF product as it awaits approval for Periodontal Defect Regeneration in India. In the other two studies Gem 21S kit (contains rhPDGF-BB), a product of Osetohealth was used. It is the only rhPDGF-BB product currently approved by FDA for periodontal defect treatment and any clinician who endeavors to use rhPDGF-BB with any scaffold material has to buy the kit as no other rhPDGF-BB alone product has been approved so far for routine dental use in North America. The kit contains 0.5mg of beta Tricalcium Phosphate
(b-TCP) and 0.3mg/ml of 0.5ml of rhPDGF-BB (sufficient for most single defects). The cost of 5 kits is US $945 at $189 each. In comparison, if b-TCP alone is used, it costs between US $ 63 to 73.6 [Table 5].

<table>
<thead>
<tr>
<th>Chemical Composition</th>
<th>Commercial Name</th>
<th>Size in gram or cubic centimeter</th>
<th>Price in U.S. $</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>b-TCP</td>
<td>Cerasorb</td>
<td>0.5</td>
<td>73.6</td>
<td>Bluesky Bio <a href="http://blueskybio.com/store/pure-phase-b-tcp">http://blueskybio.com/store/pure-phase-b-tcp</a></td>
</tr>
<tr>
<td>b-TCP</td>
<td>Premier TCP</td>
<td>0.5</td>
<td>70</td>
<td>Osseous Technologies of America <a href="http://www.osseoustech.com/promotions/2012-ao/">http://www.osseoustech.com/promotions/2012-ao/</a></td>
</tr>
</tbody>
</table>

Table 5

The kit incurs an added cost of **US $ 120 to 130** but this additional cost also yields an additional **18.1% to 39%** new bone formation (based on two multi centred clinical trials). There is no additional indirect cost associated with this health technology.

**Legal**

As per the results of our systematic search we found no relevance of Role of Platelet derived Growth Factor in Periodontal Intra-Osseous Regeneration with any ethical or legal predicament.

**Discussion**

Various GFs are currently being investigated for routine use in dental practice and hence it is of utmost importance to evaluate systematically the role of these GFs on healing of bone defects especially intra-osseous lesions. The present Health Technology Assessment Report assessed the Role of Platelet derived Growth Factor in Intra-Osseous Periodontal Regeneration. Our
systematic search resulted in 16 articles which reported clinical, radiological and/or histological evidence of new bone formation, 9 of which met the eligibility criteria and reported atleast 20% new bone formation when rhPDGF-BB was used in conjunction with scaffold material. In some of the studies, the authors reported complete regeneration of the intra-osseous defect [39, 40]. However the sample size in these studies is very small and 100% filling of the bone defects was not observed in studies with larger sample size [37, 46]. Still all the studies including 2 multi centred randomized clinical trials demonstrated significant amount of new bone formation when rhPDGF-BB was used in conjunction with scaffold material (Table 2). Interestingly though this significant difference in new bone formed due to use of rhPDGF may not guarantee a significant gain in clinical attachment level (CAL). Previously in a similar study the authors compared scaffold material alone in comparison to scaffold material with synthetic peptide [52]. They observed no significant difference in clinical parameters such as gain in clinical attachment level and reduction in mobility between the two groups although there was significant additional new bone formed with use of synthetic peptide. However these findings may not be generalizable to studies measuring the effect of other GFs such PDGF-BB because of differences in chemical composition and structure, effect on various cells and cell signalling pathways. Also, the difference in composition of scaffold material which plays a pivotal role in the whole regenerative process can influence the measured outcome as some materials have better osteoinductive, osteoconductive or osteogenic properties than others. Furthermore, some materials allow better adsorption and sustained release of proteins than others. Hence there is a great need for basic science research to elucidate the most efficient and effective carrier for delivery of proteins and growth factors such as rhPDGF-BB.
From the selected articles, we also extracted information regarding the safety of rhPDGF-BB in human subjects. Of the 16 studies that reported scientific evidence of new bone formation, 13 evaluated the safety of use of rhPDGF-BB in humans. There was no report of any serious adverse effect or complications in any of the studies and given that a good number of patients were treated with rhPDGF-BB especially in the two clinical trials, it is safe to assume that rhPDGF-BB can be used safely in human subjects without fear of complications, immunological reactions or adverse effects.

To date there is no evidence in literature to suggest that increase in additional percentage new bone formed due to use of rhPDGF-BB results in significant improvement in clinical parameters such as improvement in gingival recession, reduction in mobility, gain in clinical attachment and reduction in bleeding on probing. There is a great need for research to elucidate the clinical implications of this additional (when rhPDGF-BB is used in addition to scaffold material) bone formation and studies need to be carried out to address this issue. Furthermore there is a need for prospective clinical trials to assess: a) the effectiveness of rhPDGF-BB in conjunction with different types of scaffold materials, b) assessment of effectiveness of rhPDGF-BB with different types of scaffold material in context of clinical parameters and c) assessment of long term effectiveness of use of rhPDGF-BB in intra-osseous periodontal lesions.

Given that rhPDGF-BB incurs an additional cost of more than $ 100 and the additional bone which is formed may not significantly improve clinical parameters, our findings suggest that although it is a very promising technology, it may not be routinely used by an overwhelming majority of dentist until long term clinical trials prove significant improvement in clinical parameters associated with use of rhPDGF-BB.
## Table 1

<table>
<thead>
<tr>
<th>Authors/Year</th>
<th>Type of Study</th>
<th>Number of Patients</th>
<th>Method</th>
<th>Clinical/Histological/Radiological Evidence of New Bone Formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camello, Schenk, Nevins, Lynch and Nevins, 2003</td>
<td>Open Labelled uncontrolled clinical Study</td>
<td>4</td>
<td>0.5mg/ml rhPDGF + DFDBA in 2 patients 1.0mg/ml rhPDGF + DFDBA in 2 patients</td>
<td>Significant improvement in clinical parameters and histological evidence of new bone formation in both groups</td>
</tr>
<tr>
<td>Nevins, Giannobile, McGuire et al., 2005 [37]</td>
<td>Prospective triple blinded randomized controlled multi centre clinical trial</td>
<td>180</td>
<td>Group 1 = 0.3mg/ml rhPDGF + B-TCP Group 2 = 1.0mg/ml rhPDGF + B-TCP Group 3 = B-TCP + Buffer</td>
<td>Significant improvement in all measured clinical parameters with significantly more linear bone growth and percent defect fill in Group 1 compared to Group 3</td>
</tr>
<tr>
<td>McGuire and Scheyer, 2006 [53]</td>
<td>Open labelled split mouth design randomized clinical study</td>
<td>7 Patients</td>
<td>Test sites = rhPDGF + B-TCP with membrane Control site = sub-epithelial CTG</td>
<td>Improvement in clinical parameters with both approaches but sites treated with B-TCP+ rhPDGF were more esthetic and less bulky</td>
</tr>
<tr>
<td>Nevins, Hanratty and Lynch, 2007 [39]</td>
<td>Open labelled nonrandomized clinical study</td>
<td>2 Patients</td>
<td>Patient 1 = 0.3mg/ml rhPDGF + B-TCP Patient 2 = 1.0mg/ml rhPDGF + B-TCP</td>
<td>Significant improvement in clinical parameters and complete filling of bone defects</td>
</tr>
<tr>
<td>Fagan, Miller, Lynch and Kao, 2008 [40]</td>
<td>Open labelled uncontrolled clinical study</td>
<td>1 Patient</td>
<td>rhPDGF + FDBA</td>
<td>Clinical and histological evidence of robust bone regeneration</td>
</tr>
<tr>
<td>Ridgway, Mellonig and Cochran, 2008 [41]</td>
<td>Uncontrolled split mouth design clinical study</td>
<td>8 Patients</td>
<td>Eight sites = 0.3mg/ml rhPDGF + B-TCP Eight sites = 1.0mg/ml rhPDGF + B-TCP</td>
<td>Clinical and histological evidence of new bone formation</td>
</tr>
<tr>
<td>Simion, Rochietta, Monforte and Maschera, 2008 [54]</td>
<td>Open labelled uncontrolled clinical study</td>
<td>1 Patient</td>
<td>1.2mg/ml rhPDGF + mixture of autogenous bone and xenograft</td>
<td>Ideal osseous reconstruction with complete regeneration of bone lost in earlier surgery</td>
</tr>
<tr>
<td>Reference</td>
<td>Study Design</td>
<td>No. of Patients</td>
<td>Test Conditions</td>
<td>Control Conditions</td>
</tr>
<tr>
<td>-----------</td>
<td>--------------</td>
<td>----------------</td>
<td>----------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>McGuire, Scheyer and Schupbach, 2009 [42]</td>
<td>Randomized controlled split mouth design clinical trial</td>
<td>30 Patients</td>
<td>Test sites = 0.3mg/ml rhPDGF + B-TCP with collagen dressing</td>
<td>Control sites = sub-epithelial CTG</td>
</tr>
<tr>
<td>McGuire, Scheyer, Schupbach and Nevins, 2009 [43]</td>
<td>Open labelled controlled split mouth design clinical study</td>
<td>2</td>
<td>Test sites = rhPDGF + B-TCP with collagen dressing</td>
<td>Control sites = sub-epithelial CTG</td>
</tr>
<tr>
<td>Nevins, Camelo, Schupbach, Kim, Borges and Nevins, 2009 [45]</td>
<td>Open labelled uncontrolled randomized clinical study</td>
<td>8</td>
<td>RhPDGF + MCBS</td>
<td></td>
</tr>
<tr>
<td>Jayakumar et al., 2011 [46]</td>
<td>Double blinded controlled parallel prospective multi centre clinical trial</td>
<td>54</td>
<td>Group 1 = rhPDGF + B-TCP</td>
<td>Group 2 = B-TCP alone</td>
</tr>
<tr>
<td>Nevins, Camelo, Kim, Schupbach, Kim, and Nevins, 2011 [55]</td>
<td>Open labelled parallel randomized clinical study</td>
<td>16</td>
<td>Group 1 = MCBS</td>
<td>Group 2 = MCBS + rhPDGF</td>
</tr>
<tr>
<td>Rosen and Holzclaw, 2011 [49]</td>
<td>Retrospective Chart Review</td>
<td>50</td>
<td>rhPDGF + FDBA</td>
<td></td>
</tr>
<tr>
<td>McAllistar, Haghighat, Prasad and Rohrer, 2010 [56]</td>
<td>Open labelled randomized uncontrolled clinical study</td>
<td>11</td>
<td>Group 1 = 0.5ml rhPDGF + PDGF</td>
<td>Group 2 = 0.5ml rhPDGF + xenograft</td>
</tr>
</tbody>
</table>
| Nevins, Camelo, Nevins, Schenk and Lynch, 2003 [31] | Open labelled uncontrolled clinical study | 9 | Sites for Group 1 = 0.5mg/ml rhPDGF + DFBDA  
Sites for Group 2 = 1.0mg/ml rhPDGF + DFBDA  
Sites for Group 3 = 5.0mg/ml rhPDGF + DFBDA  
Sites for Group 4 = xenograft with collagen dressing | Sites treated with rh PDGF + DFBDA showed significant improvement in clinical parameters with histological evidence of new bone formation |
### Table 2

<table>
<thead>
<tr>
<th>Authors/Year</th>
<th>Type of Study</th>
<th>Number of Patients</th>
<th>Method</th>
<th>Effectiveness as Measured by Percentage of New Bone Formed</th>
</tr>
</thead>
</table>
| Nevins, Giannobile, McGuire et al., 2005  | Prospective Triple Blinded Randomized Multi Centre Clinical Trial | 180                | Group 1 = 0.3mg/ml rhPDGF + B-TCP 
Group 2 = 1.0mg/ml rhPDGF + B-TCP 
Group 3 = B-TCP + Buffer                  | Mean new bone formed within the osseous lesion for Group 1 = 57%, Group 2 = 34% and Group 3 = 18% |
| Nevins, Hanratty and Lynch, 2007 [39]     | Open labelled nonrandomized clinical study              | 2 Patients         | Patient 1 = 0.3mg/ml rhPDGF + B-TCP 
Patient 2 = 1.0mg/ml rhPDGF + B-TCP                                                     | Complete filling of osseous defect (100%) was observed in both patients |
| Fagan, Miller, Lynch and Kao, 2008 [40]   | Open labelled uncontrolled clinical study               | 1 Patient          | rhPDGF + FDBA                                                                            | Complete filling of the osseous defect measured as horizontal bone defect (100%) |
| Simion, Rochietta, Monforte and Maschera, 2008 [54] | Open labelled uncontrolled clinical study         | 1 Patient          | 1.2mg/ml rhPDGF + mixture of autogenous bone and xenograft                              | Complete regeneration of bone lost in earlier surgery (100%) |
| Nevins, Camelo, Schupbach, Kim, Borges and Nevins, 2009 [45] | Open labelled randomized uncontrolled clinical study | 8                  | Group 1 = rhPDGF + MCBS with surgical re-entry at 4 months 
Group 2 = rhPDGF + MCBS with surgical re-entry at 6 months                                  | Mean new bone formed in Group 1 = 23.2% and in Group 2 = 18.2% |
| Jayakumar et al., 2011 [46]               | Double Blinded Controlled Parallel Prospective Multi Centre Clinical Trial | 54                 | Group 1 = rhPDGF + B-TCP 
Group 2 = B-TCP alone                                                                       | Percentage of mean new bone formed within the osseous defect for Group 1 = 65.6% and for Group 2 = 47.5% |
| Nevins, Camelo, Kim, Schupbach, Kim, Nevins, 2011 [55] | Open labelled parallel randomized clinical study             | 16                 | Group 1 = MCBS 
Group 2 = MCBS + rhPDGF 
Group 3 = MCBS + EMD                                                           | Percentage of mean new bone formed in Group 1 = 28.3%, Group 2 = 39.6%, Group 3 = 23.9% and Group 4 = 21.4% |
| McAllistar, Haghighat, Prasad and Rohrer, 2010 [56] | Open labelled randomized uncontrolled clinical study | 11 | Group 1 = 0.5ml rhPDGF + PDGF  
Group 2 = 0.5ml rhPDGF + xenograft | Percentage of mean new bone formation in Group 1 = 21% and in Group 2 = 24% |
| Nevins, Camelo, Nevins, Schenk and Lynch, 2003 [31] | Open labelled uncontrolled clinical study | 9 | Sites for Group 1 = 0.5mg/ml rhPDGF + DFDBA  
Sites for Group 2 = 1.0mg/ml rhPDGF + DFDBA  
Sites for Group 3 = 5.0mg/ml rhPDGF + DFDBA  
Sites for Group 4 = xenograft with collagen dressing | Mean percentage gain in bone in sites treated with rhPDGF + DFDBA was 28.99% |
### Table 3

<table>
<thead>
<tr>
<th>Authors/Year</th>
<th>Type of Study</th>
<th>Number of Patients</th>
<th>Method</th>
<th>Serious Adverse Effects/Complications other than Surgical Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camello, Schenk, Nevins, Lynch and Nevins, 2003 [11]</td>
<td>Open Labelled uncontrolled clinical Study</td>
<td>4</td>
<td>0.5mg/ml rhPDGF + DFDBA in 2 patients</td>
<td>All sites healed uneventfully</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.0mg/ml rhPDGF + DFDBA in 2 patients</td>
<td></td>
</tr>
<tr>
<td>Nevins, Giannobile, McGuire et al., 2005 [37]</td>
<td>Prospective Triple Blinded Randomized Controlled Multi Centre Clinical Trial</td>
<td>180</td>
<td>Group 1 = 0.3mg/ml rhPDGF + B-TCP</td>
<td>No serious adverse effects attributable to any treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Group 2 = 1.0mg/ml rhPDGF + B-TCP</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Group 3 = B-TCP + Buffer</td>
<td></td>
</tr>
<tr>
<td>McGuire and Scheyer, 2006 [53]</td>
<td>Open labelled split mouth design randomized clinical study</td>
<td>7 Patients</td>
<td>Test sites = rhPDGF + B-TCP with membrane</td>
<td>No adverse effects reported with any treatment modality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Control site = sub-epithelial CTG</td>
<td></td>
</tr>
<tr>
<td>Nevins, Hanratty and Lynch, 2007 [39]</td>
<td>Open labelled nonrandomized clinical study</td>
<td>2 Patients</td>
<td>Patient 1 = 0.3mg/ml rhPDGF + B-TCP</td>
<td>No complications or adverse effects recorded</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patient 2 = 1.0mg/ml rhPDGF + B-TCP</td>
<td></td>
</tr>
<tr>
<td>Ridgway, Mellonig and Cochran, 2008 [41]</td>
<td>Uncontrolled split mouth design clinical study</td>
<td>8 Patients</td>
<td>Eight sites = 0.3mg/ml rhPDGF + B-TCP</td>
<td>Excellent soft tissue healing in all but one subject</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Eight sites = 1.0mg/ml rhPDGF + B-TCP</td>
<td></td>
</tr>
<tr>
<td>Simion, Rochietta, Monforte and Maschera, 2008 [54]</td>
<td>Open labelled uncontrolled clinical study</td>
<td>1 Patient</td>
<td>1.2mg/ml rhPDGF + mixture of autogenous bone and xenograft</td>
<td>Excellent tissue appearance and healing without dehiscence</td>
</tr>
<tr>
<td>McGuire, Scheyer and Schupbach, 2009 [42]</td>
<td>Randomized controlled split mouth design clinical trial</td>
<td>30 Patients</td>
<td>Test sites = 0.3mg/ml rhPDGF + B-TCP with collagen dressing</td>
<td>No serious adverse effects or complications were reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Control sites = sub-epithelial CTG</td>
<td></td>
</tr>
<tr>
<td>Study References</td>
<td>Study Design</td>
<td>Sample Size</td>
<td>Treatment</td>
<td>Outcomes</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-------------</td>
<td>------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Mellonig, Valderrma and Cochran, 2009 [44]</td>
<td>Open labelled uncontrolled clinical study</td>
<td>4</td>
<td>rhPDGF + B-TCP with collagen dressing</td>
<td>Uneventful healing reported in all patients</td>
</tr>
<tr>
<td>Nevins, Camelo, Schupbach, Kim, Borges and Nevins, 2009 [45]</td>
<td>Open labelled uncontrolled randomized clinical study</td>
<td>8</td>
<td>RhPDGF + MCBS</td>
<td>Uneventful healing reported in all subjects</td>
</tr>
<tr>
<td>Jayakumar et al., 2011 [46]</td>
<td>Double Blinded Controlled Parallel Prospective Multi Centre Clinical Trial</td>
<td>54</td>
<td>Group 1 = rhPDGF + B-TCP</td>
<td>No serious adverse effects or complications observed with any treatment modality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Group 2 = B-TCP alone</td>
<td></td>
</tr>
<tr>
<td>Nevins, Camelo, Schupbach, Kim, Kim and Myron Nevins, 2011 [55]</td>
<td>Open labelled parallel randomized clinical study</td>
<td>16</td>
<td>Group 1 = MCBS</td>
<td>Uneventful healing in all subjects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Group 2 = MCBS + rhPDGF</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Group 3 = MCBS + EMD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Group 4 = EMD + Bone ceramic</td>
<td></td>
</tr>
<tr>
<td>McAllistar, Haghighat, Prasad and Rohrer, 2010 [56]</td>
<td>Open labelled randomized uncontrolled clinical study</td>
<td>11</td>
<td>Group 1 = 0.5ml rhPDGF + PDGF</td>
<td>No postoperative complications were recorded</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Group 2 = 0.5ml rhPDGF + xenograft</td>
<td></td>
</tr>
<tr>
<td>Nevins, Camelo, Nevins, Schenk and Lynch, 2003 [31]</td>
<td>Open labelled uncontrolled clinical study</td>
<td>9</td>
<td>Sites for Group 1 = 0.5mg/ml rhPDGF + DFDBA</td>
<td>No adverse effects or complications were recorded</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sites for Group 2 = 1.0mg/ml rhPDGF + DFDBA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sites for Group 3 = 5.0mg/ml rhPDGF + DFDBA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sites for Group 4 = xenograft with collagen dressing</td>
<td></td>
</tr>
</tbody>
</table>
### Table 4

<table>
<thead>
<tr>
<th>Authors/Year</th>
<th>Type of Study</th>
<th>Number of Patients</th>
<th>Follow Up Time</th>
<th>Method</th>
<th>Effectiveness as Measured by Percentage of New Bone Formed</th>
</tr>
</thead>
</table>
| Nevins, Giannobile, McGuire et al., 2005 [37] | Prospective Triple Blinded Randomized Controlled Multi Centre Clinical Trial | 180 | 6 Months | Group 1 = 0.3mg/ml rhPDGF + B-TCP  
Group 2 = 1.0mg/ml rhPDGF + B-TCP  
Group 3 = B-TCP + Buffer | Mean new bone formed within the osseous lesion Group 1 = 57%, Group 2 = 34% and Group 3 = 18% |
| Jayakumar et al., 2011 [46] | Double Blinded Controlled Parallel Prospective Multi Centre Clinical Trial | 54 | 6 Months | Group 1 = rhPDGF + B-TCP  
Group 2 = B-TCP alone | Percentage of mean new bone formed within the osseous defect for Group 1 = 65.6% and for Group 2 = 47.5% |
| Nevins, Camelo, Nevins, Schenk and Lynch, 2003 [55] | Open labelled parallel randomized clinical study | 16 | 5 Months | Group 1 = MCBS  
Group 2 = MCBS + rhPDGF  
Group 3 = MCBS + EMD  
Group 4 = EMD + Bone ceramic | Percentage of mean new bone formed in Group 1 = 28.3%, Group 2 = 39.6%, Group 3 = 23.9% and Group 4 = 21.4% |
Articles addressing role of PDGF in Intra-Osseous Periodontal Regeneration
21 Titles

Effectiveness

Studies demonstrating Clinical/Histological/Radiological evidence of new bone formation
16 Titles
[9 Titles reported percentage of new bone formed]

Studies which assessed safety
13 Titles

Safety

Studies comparing graft material + PDGF with graft material alone
3 Titles

Cost Analysis

Overview of Findings of Selected Articles
References

53. McGuire, M.K. and E.T. Scheyer, Comparison of recombinant human platelet-derived growth factor-BB plus beta tricalcium phosphate and a collagen membrane to subepithelial connective

