ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

EFFECT OF MINERAL TRIOXIDE AGGREGATE AS A ROOT END FILLING MATERIAL ON PERIODONTAL LIGAMENT CELLS ,CEMENTOGENESIS AND PERIRADICULAR BONE REGENERATION– A LITERATURE REVIEW

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Manuscript Info

Manuscript History:

Received: 15 July 2015
Final Accepted: 30 August 2015
Published Online: September 2015

Key words:

mineral trioxide aggregate; periodontal ligament cells, peri radicular healing; bone regeneration

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Abstract

The purpose of this paper is to review the constituents, setting reaction, biocompatibility, cellular reactions and regenerative Potential of Mineral Trioxide Aggregate (MTA) as a root-end filling material. This paper also reviews the newer root end materials and their biocompatibility in comparison to MTA.The first publication on the material was in November 1993. Hence anelectronic search of scientific papers from November 1993 to July 2015 was done using databases MEDLINE-PubMed, Cochrane-CENTRAL and EMBASE search engines to include relevant scientific citations from the peer-reviewed journals published in English.. Specific searches on constituents, setting reaction and interaction of MTA with the periradicular tissue,biocompatibility of MTA retrograde filling material, cellular reaction to periodontal ligament cells andbone regeneration cells was accomplished. Based on the assessment and screening of the papers, it can be concluded that MTA showed minimal inflammatory reactions, survival of periodontal ligament cells, presence of consistent cementum and goodbone healing potential.

INTRODUCTION

Endodontic surgery is an important adjunct to conservative root canal treatment. It is performed to resolve inflammatory processes that cannot be successfully treated by conventional techniques, which may be due to complex canal and/or apical anatomy and external inflammatory processes . Surgical procedures may also be indicated for the resolution of procedural misadventures, to include root perforation that may occur either during canal instrumentation or post-space preparation and is sometimes the only option for some endodontic conditions. Surgical treatment usually involves the placement of a material thatis capable of being adapted as closely as possible to the dentinal walls of the root-end preparation in order to seal the root canal contents from the periradicular tissues and repair the root defects.[1]

The main goal of a root-end filling material is to provide an apical seal to prevent the movement of bacteria and the diffusion of bacterial products from the root canal system into the periapicaltissues.[2]Gartner & Dorn (1992)[3] proposed that an ideal root-end filling material should be easy to manipulate,be radiopaque, dimensionally stable,nonresorbable, insensitive to moisture, impervious to dissolution or breakdown by the tissue fluids, adhesive to dentine, nontoxic,biocompatible and provide periradicular tissues healing.[3]

The ability to promote periapical healing could be particularly beneficial. Periapical healing involves the repair and regeneration of alveolar bone and the periodontal ligament.[4]To optimize the healing potentials, it would be preferable to use a dental material that would promote the restoration of the original architecture of the destructed

periodontal apparatus. Specifically, it would be favourable to use a material that may stimulate cementogenesis, which is considered essential for the regeneration of a functional periodontal ligament (PDL) (Schallhornet al. 1970, Sch€upbach et al. 1993, Grzesik& Narayanan 2002).[5]

A plethora of restorative and endodontic materials have been suggested over the years for root-end filling, including amalgam, zinc oxide eugenol (ZOE) cement (plain or reinforced), ethoxy benzoic acid (EBA) and Super EBA cement, polycarboxylate cement, glass ionomercement (GIC), gutta-percha (GP, burnished or injectable), composite resin, cyanoacrylate glue, Teflon, gold foil, titanium screws, Cavit, and a number of newly introduced materialssuch as Mineral Trioxide Aggregate (MTA).[6]

MTA may be the ideal material for use against bone, because it is the only material that consistently allows for the overgrowth of cementum and formation of bone, and it facilitates the regeneration of the periodontal ligament.[7] Much work has been published on the biocompatibility of this material, but relatively little on its effect on PDL cells, cementogenesis and alveolar bone healing. Hence the purpose of this systematic review was to compile and assess whether MTA root end restoration leads to regeneration of the adjacent periodontal tissues.

METHODOLOGY

An electronic search of scientific papers was accomplished using MEDLINE-PubMed, Cochrane-CENTRAL and EMBASE databases using selected keywords and with appropriate medical subject headings (MeSH). The search terms (keywords/headings) used were: Mineral Trioxide Aggregate (MTA); White MTA (WMTA); Gray MTA (GMTA); properties of MTA (physical, chemical, bacterial, biological, biocompatibility); periapical surgery; retro-filling materials; root-end filling materials; periradicular healing; periodontal ligament cells; osteoblastic activity; bone regeneration; newer formulations of MTA; recent advances in root-end filling materials. Only articles relevant to the topic (MTA) and published in English in peer-reviewed journals from November 1993 to July 2015were included. Following this, a hand-search was conducted for the available issues of all the major journals pertaining to the topic.

PERIRADICULAR SURGERY –MECHANISM OF HEALING AND REPAIR

Resection of the root end during peri radicular surgery results in an exposed apical dentine surface bounded by cementum with a root canal at its centre.[8]Surgical treatment usually involves the placement of a material that is capable of being adapted as closely as possible to the dentinal walls of the root-end preparation in order to seal the root canal contents from the periradicular tissues and repair the root defects.[9]

Unlike orthograde root canal filling materials; root-end filling materials are placed in direct contact with vital periapical tissues. The tissue response to these materials, therefore, becomes important and may influence the outcome of surgical endodontic treatment.[6] Important criteria to judge success of surgical endodontic treatment is to confirm bone regeneration at apical lesion. Healing after apical surgery includes dento alveolar healing and alveolar healing. Dentoalveolar healing is regeneration of apical attachment apparatus while alveolar healing is osseous repair of medullary and cortical bone.[10]

The healing of injured tissue in the peridontium is clearly dependent on the biocompatibility of the repair material and cells interaction with them. It has been demonstrated that the migration and differentiation of multipotent mesenchymal stem cells during the bone and periodontal healing and regeneration process are necessary.[11]

Immunohistochemical analyses and in situ hybridization experiments have been used to reveal that mesenchymal cells, including osteoblasts, express morphogenetic bone proteins (BMP) and receptors (BMPR) during the formation of skeletal and fracture repair bone tissue. These glycoproteins are responsible for bringing osteoprogenitor cells to bone formation and repair sites and thus have important implications in cascades of cellular events that regulate bone formation and repair. During these processes, mesenchymal cells induce cell proliferation and differentiation, and promote the synthesis of the extracellular matrix. As a result, BMPs are involved in the differentiation process wherein osteoprogenitor cells transform into mature osteoblasts. The cellular response to BMP depends not only on the expression of type of protein but also of the expression and location of the surface transmembrane receptors BMPR type 1A, 1B, and type 2. All these factors collectively exhibit features that can help the bone formation process when MTA is used.[12]

The most ideal healing outcome after filling the resected root canal would be reformation of a normal attachment apparatus with healthy bone, periodontal ligament, and cementum. Hence, the ultimate goal of treatment root-end surgery is to maintain or re-establish the damaged attachment apparatus.[13]

Bone regeneration depends on differentiation of osteoblasts and synthesis and mineralization of extracellular bone matrix.[6]The deposition of cementum on the cut root face is considered a desired healing response and a prerequisite

for the reformation of a functional periodontal attachment.Cementum deposition occurs from the circumference of the root-end and proceeds centrally toward the resected root canal. The cementum provides a 'biological seal,' in addition to the 'physical seal' of the root-end filling, thereby creating a 'double seal'.[6]

MINERAL TRIOXIDE AGGREGATE (MTA) –CONSTITUENTS AND SETTING REACTION.

MTA was introduced in 1993 by Loma Linda University as a possible root-end filling material or for repair of lateral root perforations. The principal components of MTA are tricalcium oxide, tricalcium silicate, bismuth oxide, dicalcium silicate, tricalcium aluminate, tetracalciumaluminoferrite, and calcium sulfate dihydrate.White MTA (WMTA) differs from gray-colored MTA (GMTA) in that it has a significant reduction in the proportion of the tetracalciumaluminoferrite component.[14]

MTA consists of fine hydrophilic particles that form a colloidal gel in the presence of water. After mixing, hydration takes place and the oxides in MTA dissolve, locally releasing hydroxyl and metal ions. This leads to a drastic pH elevation (Torabinejad et al.1995)[15] The initial pH of MTA is 10.2, with an increase to 12.5, 3 hours after mixing.Calcium hydroxide is the main compound released by MTA in water.[8]The released calcium ions (Maeda et al. 2010)[16] react with the CO_2 found in the tissues to produce crystalline calcium carbonate (Holland et al. 2002).[17] Other authors have suggested that the released calcium ions react with phosphorous ions found in the tissue fluids to produce a layer of hydroxyapatite crystals over MTA.Gandolfi et al. 2010).[18]

MTA offers a biologically active substrate for bone cells and stimulates interleukin production because of its alkaline pH and calcium ion release The initially severe inflammatory response to MTA is most likely multifactorial with high pH, heat generated during setting and the generation of inflammatory cytokines such as interleukin-1 and interleukin-6 contributing to the process Furthermore, the formation of calcium hydroxide during the setting of MTA explains the high pH of the set material[8] .The basic framework of the hydrated set mass is formed by the interlocking of cubic and needle-like crystals in which the needle-like crystals form in sharply delineated thick bundles that fill the inter-grain space between the cubic crystals .[1]The biologic activity of MTA is attributed to the high pH level associated with formation of calcium hydroxide. Current studies indicated that the biological activity of MTA is attributed to the formation of hydroxyapatite-like precipitate on its surface. GMTA was observed to produce twice as much hydroxyapatite crystals as WMTA, suggesting different levels of bioactivity of the two materials.The HA-layer also creates a chemical bond between MTA and the dentinal walls. The particle size and dimensional shape of MTA can also occlude dentinal tubules,MTA provides a good biological seal and can act as a scaffold for the formation and/or regeneration of hard tissue (periapical).[19]Studies evaluating MTA as a retrofilling material have shown less periapical inflammation, presence of a fibrous capsule and formation of new cementum layer in contact with the material surface in many cases.[20]

CELLULAR REACTIONS TO MTA-A BASIS FOR ITS BIOACTIVITY

Mesenchymal stem cells play an important role in tissue and bone remodeling, and differentiation of mesenchyme-derived stem cells are thought to be affected by the local environmental factors.[11]

Animal and human studies have shown minimal or no inflammation to bone and connective tissue following implantation of MTA. When used (in a canine model) for root-end restoration or for the repair of lateral/furcation perforation, MTA has shown favorable healing characteristics, such as lack of inflammation, no ankylosis, cellular cementum formation (overgrowth), and PDL regeneration between the cementum and alveolar bone.[19]

Enhanced attachment and proliferation of periodontal ligament and gingival fibroblasts were observed on the set-surfaces of MTA. Similarly, cell cultures studies (animal and human) using human alveolar bone cells, mouse preosteoblasts, osteoblasts, dentinoblasts, and mouse cementoblasts have shown good survival, proliferation, and attachment, with a faster and better growth of cells on the MTA surface.[19]

Patrícia Yoshino et al[21] conducted a study on the cytotoxicity of White MTA on Human Periodontal Ligament Fibroblasts and concluded that MTA did not show cytotoxic activity over cultured periodontal ligament fibroblasts.

Animal cells (rat bone marrow cells, mouse pre osteoblasts) and human cells (gingival fibroblasts, periodontal ligament fibroblasts, alveolar bone cells) exposed to MTA have been shown to express alkaline phosphatase, bone sialoprotein, periostin, and osteocalcin, along with the formation of extensive collagenous matrix.[19]Intra-osseous implantation of MTA showed a relatively mild-to-minor inflammatory response, which is more favorable compared to amalgam, super EBA, and IRM.[19]

McNamara et al.[22] reported that grey-colored MTA displays no inflammation at 8-week implantation into rat mandibles. In a dog's teeth model grey-colored MTA was associated with less periapical inflammation and tissue response, even when no root filling or coronal restoration was present.[23]Cintra et al.[24] found an MTA implant

specimen showing irregular basophilic areas and hard tissues in close contact to the material after one-month implantation in alveolar bone of rats. MTA does not produce any adverse effect on the microcirculation of the connective tissue but it could speed up the bone healing process.[25]

Again, MTA (ProRoot) supported almost complete regeneration of the periradicularperiodontium when used as a rootend filling material on noninfected teeth (Regan et al. 2002).[26]The most characteristic tissue reaction to MTA was the presence of organizing connective tissue with occasional signs of inflammation after the first postoperative week (Economides et al. 2003).[27]

In their comprehensive 2004 study, Bonson and colleagues[28] used human gingival fibroblasts and periodontal ligament fibroblasts, the latter of which possess some osteogenic potential. The periodontal ligament fibroblasts that were exposed to MTA expressed osteoblast-associated proteins such as alkaline phosphatase, bone sialoprotein and periostin.

Likewise, we found that human alveolar bone cells grown on MTA disks in vitro expressed type I collagen and synthesized an extensive collagenous matrix during 2 weeks of growth.[29]Concomitantly, the osteoblast specific transcription factor Runx2 was expressed within a week of culture on MTA. Furthermore, this pattern of gene expression was largely unaltered by interactions with alternative formulations of MTA.[4]

In an investigation of 2012 Al-Hiyasat et al.[30] observed the quality of cellular attachment to various root-end filling materials and concluded that the best cellular attachment of fibroblasts can be observed on the surface of MTA, whereas Super EBA surfaces did not attract cell adherence most likely due to the leaking of eugenol into the dentinal tubules. Unwashed glass ionomer cement surfaces did not induce cell attachment either[30];MTA are able to develop a hydroxyl apatite-like surface in the presence of body liquids containing calcium or phosphate. This surface is biocompatible and displays good conditions for cell attachment and proliferation.[13]

In a study by Jung et al.[13] on human oral cells' response to different endodontic restorative materials he concluded thatProRoot MTA and Biodentine showed no cytotoxicity and a good biocompatibility in direct contact with osteoblasts and PDL cells. Regarding cell survival and proliferation particularly of PDL cells Biodentine showed good results and can be considered as awell-tolerated endodontic material with stimulatory bioactive properties.[13]

A number of in vitro and in vivo studies have proven that MTA has no cellular or tissue toxicity (Saidon et al. 2003, Ribeiro et al. 2006)[31,32] Furthermore, later studies have demonstrated that human periodontal fibroblasts, when cultured with MTA, present attachment normal growth and functions (Lin et al. 2004, Hakki et al. 2012)[33,34]and have shown cellular signal transduction stimulation and expression of genes encoding for bone morphogenetic protein-2 (BMP-2), calciumsensing reactor (Maeda et al. 2010)[16], alkaline phosphataseand collagen type I (Yan et al. 2010).[35] These events show that incubation with MTA can induce differentiation of human PDL fibroblasts. Similarly, osteoblast cell cultures were observed to grow when in contact with MTA, and they displayed elevated interleukin expression and osteocalcin and alkaline phosphatase In addition, MTA stimulated the expression of osteocalcin, collagen type I, alkaline phosphatase, and bone sialoprotein in cementoblast cell cultures.[36]

From the aforementioned in vitro studies, it seems that MTA may demonstrate a cellular effect that is broader than that of an inert material. MTA appears to be a material with potent biological activity, specifically in osteogenic and cementogenicdirections (Bonson et al. 2004, Maeda et al. 2010).[16,28] MTA's biological activity may regulate some of the major events required for the regeneration of the attachment apparatus.[36]Studies further reported that the ligament fibres were well organized, and described that in some cases, the PDL fibres inserted in the newly formed cementum.[36]

CEMENTOGENIC CAPACITY OF MTA

MTA has the capacityto induce bone, dentin, and cementum formation and regeneration of periapical tissues (periodontal ligament and cementum). It is ancementogeniccementoconductive and cementoinductive agent. MTA stimulates immune cells to release lymphokines and bone coupling factors required for the repair and regeneration of cementum and healing of osseous periapical defects.[19]

Cementogenesis is considered essential for the regeneration of a functional PDL (Schallhorn et al. 1970, Sch€upbach et al. 1993, Grzesik& Narayanan 2002). All of the selected studies described cementum formation in contact with MTAShort-term in vitro studies have shown cementoblast adhesion and expression of mineralization-associated genes in contact with MTA (Thomson et al. 2003). The link between material properties and cementogenesis can only be assumed. The presence of alkaline pH and calcium ions is considered essential for calcified tissue formation (Lundgren et al. 1992). After mixing the MTA, the release of both (hydroxyl and calcium) ions is maximal, while after 4 days, it plateaus (Duarte et al. 2003). This course of ion levels may be associated with the more favourablecementum formation in contact with freshly mixed MTA (#2).

From the histological results,From studies 21Cementogenesis over MTA occurred consistently within a longer observation time frame of 3–6 months, at the end of which it occurred in almost all specimens. Bacterial

contamination has the potential to induce periradicular inflammation (Kakehashi et al. 1965, Lin et al. 2006) and is of importance for the healing and regenerative potential of the periradicular tissues (Fabricius et al. 2006).In summary, it appears that cementum formation after MTA placement has an inverse relationship with periradicular inflammation. A possible explanation might be that periapical inflammation has been linked to acidic pH values (Tronstad et al. 1981, McCormick et al. 1983). This may have a detrimental effect on the setting reaction, crystal formation, and mechanical properties of MTA (Lee et al. 2004), possibly affecting its cementogeniccapacityIn the selected studies, the presence of cementum was combined with the presence of periodontal ligament with inserting Sharpey'sfibres (#16, 22). The ligament space was not always well organized. Residual inflammation (#6) and MTA overfilling (#12) were linked to a partially organized PDL. Alveolar bone, the third component of the periodontium, also showed favourable histological or microradiographic (#5) response after MTA placement.

Thepossible difference in cementogenic capacity between fresh and set MTA was tested in study #2.

Cementum was deposited in contact with "fresh" material in all 12 cases and with "set" material in 8 of 12 of the cases.In study #15, cementum deposition was observed on 73.1% (SD 38.1%) of the MTA surface.study #18, where it was reported that the presence of a complete cemental covering of the filling material was variable and unpredictable.[36]

Bone fill of the defects was consistent, although its extent was, in most cases, not quantified In the selected studies, the presence of cementum was combined with the presence of periodontal ligament with inserting Sharpey'sfibres (#16, 22). The ligament space was notalways well organized. Residualinflammation (#6) and MTA overfilling(#12) were linked to a partiallyorganized PDL. Alveolar bone, the third component of the periodontium, also showed favourable.[36]

In addition, the presence of cementum on the surface of MTA (Loma Linda University) was a frequent finding (Torabinejad et al. 1997).Both fresh and set MTA (ProRoot) caused cementum deposition when used after apical surgery (Apaydin et al. 2004). In addition, MTA (ProRoot) showed the most favourableperiapical tissue response of three materials tested, with formation of cemental coverage overMTA(Baek et al. 2005.[37]

Dreger et al[38] reported that calcium silicate-based MTA or Portland cements released some of their components in the tissue capable of stimulating mineral deposition in the cement-dentin interface and in the interior of the dentinal tubules.

Do Nascimento, et al., 2008[39] revealed that the deposition of hard tissue on the MTA is related to sealing ability, biocompatibility, and alkaline pH; the presence of calcium and phosphate of ions in their formulation; and the ability to attract blast cells and promote a favorable environment for cementum formation.[14]

HARD TISSUE FORMATION AND BONE REGENERATION POTENTIAL OF MTA

Hard tissue formation over the root-end filling material requires the process of cell differentiation into hard tissue-forming cells and activation of the mineralization process.[11]

MTA has the capacity to induce bone.It is an osteoconductive, osteoinductive agent. MTA stimulates immune cells to release lymphokines and bone coupling factors required for the repair and regeneration of cementum and healing of osseous periapicaldefects.MTA can also stimulate periodontal ligament fibroblasts to display osteogenic phenotype and produce osteonectin, osteopontin, and osteonidogen. Cell culture studies have shown an up-regulation of various cytokines, biological markers, and interlukines, like IL-1α, IL-1β, lL-4, IL-6, osteocalcin, alkaline phosphatase, bone sialoprotein, osteopontin, BMP-2, PGE2, and cyclooxygenase-2, by MTA.[19] which may actively promote hard-tissue formation.[9]

The bone regenerating capacity of MTA is attributable to the release of hydroxyl ions and formation of calcium hydroxide during the hydration process.[19]Concerning the hydroxyl ion concentration, its higher levels have been directly correlated with altered extracellular matrix organization, reduced ALP activity, and bone-like nodule formation in osteogenic cell cultures .[18]During bone matrix mineralization, ALP generates the inorganic phosphate needed for hydroxyapatite crystallization and might also hydrolyze pyrophosphate, a mineralization inhibitor, to facilitate mineral precipitation and growth.[40]

Other reports had observed the formation of a white interfacial material (precipitates) between GMTA and tooth structure within 1 to 2 hours when exposed to physiologic fluids (phosphate-buffered physiologic solution) in vivo or with simulated body fluids in vitro. SEM and x-ray diffraction (XRD) analysis of these precipitates revealed the presence of chemically and structurally similar hydroxyapatite (HA)-like structure with a chemical composition of oxygen, calcium, and phosphorus, along with trace amounts of bismuth, silicon, and aluminum.However, the calcium-to-phosphorus ratios reportedly differed from that of natural hydroxyapatite. This HA-like structure can release calcium and phosphorus continuously, promoting the regeneration and remineralization of hard tissues and increasing the sealing ability of MTA.Thus, release of hydroxyl ions, a sustained high pH for extended periods,

modulation of cytokine production, formation of calcium hydroxide, and a mineralized interstitial layer (HA) may be responsible for the excellent biocompatibility and biological bone regeneration activity of the material.[19]
Whereas slightly higher extracellular calcium concentration than physiological values has been shown to stimulate osteoblast cell viability, proliferation, differentiation, and function cellular calcium overload can cause cytotoxicity and trigger either apoptotic or necrotic cell death.[40]
When MTA (Loma Linda University) has been used for root-end filling in vivo, less periradicular inflammation was reported compared with amalgam (Torabinejad et al. 1995d It induced apical hard tissue formation with significantly greater consistency, but not quantity.[15]
In a study of three materials,Shabahang et al concluded that MTA can induce the formation of apical hard tissue with significantly greater consistency than osteogenic protein-1 and calcium hydroxide.[41]
Early tissue healing events after MTA root-end filling were characterized by hard tissue formation, activated progressively from the peripheral root walls along the MTA–soft tissue interface (Economides et al. 2003).[23]
Use of MTA (ProRoot) in combination with calcium hydroxide in one study has shown that the periodontium may regenerate more quickly than either material used on its own in apexification procedures (Ham et al. 2005). All these studies in vivo have shown a favourable tissue response to MTA.[42]
Bortoluzzi et al[43] suggested that WMTA could lead to formation of calcite granules and underlying bridges of mineralized tissue because of the release of calcium ions that react with the carbonate of the tissues. Xu et al[44] found that newly formed bone tissue grew into the porous calcium silicate-based materials in a rabbit calvarial defect model, along with the deposition of a bone-like apatite layer at the tissue/material interface.
Similarly, Nakayama and colleagues[45] found expression of alkaline phosphatase and osteopontin by rat femoral bone marrow cells exposed to MTA. More recently, Tani-Ishii and colleagues[46] detected the expression of bone sialoprotein and osteocalcin from mouse MC3T3-E1 preosteoblasts exposed to MTA.
It was demonstrated that MTA induces bone morphogenetic protein 2 expression and calcification in human periodontal ligament cells and stimulating human gingival fibroblasts to produce BMP-2, is able to promote a favorable formation of mineralized tissue in rat alveolar sockets, being characterized by mild inflammatory response and complete bone healing. MTA surfaces also support osteoblast cell attachment, matrix synthesis and RunX2 expression which are essential for osteogenesis.[12]
In addition to stimulating adhesion and cell proliferation18, the expression of alkaline phosphatase by fibroblasts,4 osteocalcin and other interleukins by osteoblasts. MTA was able to induce a greater expression of the BMPR-1B receptor, which is important in the process of osteogenesis, being directly involved in the process of bone condensation.[12]
Do Nascimento, et al, 2008[39] The author reported that the osteoconductive effect, stimulation of the proliferation and cell adhesion, stimulation of the expression of alkaline phosphatase by fibroblasts and osteocalcin and other interleukins by osteoblasts, are also characteristics related to this material. These findings may help to explain the higher area of the formation of osteoid tissue and bone in the MTA group and MTA+BCP observed in this work.

Conclusion

MTA is a promising material with an expanding foundation of research. To date, however, the majority of the work has been done by Torabinejad and colleagues, who were involved in the material's development.Their research is very thorough and compelling, but there is a need for more studies by independent researchers. In addition,
there have been no published human studies withMTA. Impressive results in animal models do not always
translate into impressive results in humans, so there is a need for controlled clinical studies on humans. Several of the cases presented in this article have follow-up periods of less than one year. The success of a new material can best be judged with long-term studies.[7]

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