Prospects of Advanced Therapy Medicinal Products–Based Therapies in Regenerative Dentistry: Current Status, Comparison with Global Trends in Medicine, and Future Perspectives

ABSTRACT

Introduction: Regenerative medicine offers innovative approaches to restore damaged tissues on the basis of tissue engineering (TE). Although research on advanced therapy medicinal products (ATMPs) has been very active in recent years, the number of licensed products remains surprisingly low and restricted to the treatment of severe, incurable diseases. Methods: This paper provides a critical review of current literature on the regulatory, clinical, and commercial status of ATMP-based therapies in the EU and worldwide and the hurdles to overcome for their broader application in Regenerative Dentistry. Results: Competent authorities have focused on developing regulatory pathways to address unmet patient needs. Oncology represents the dominating field, followed by cardiovascular, musculoskeletal, neurodegenerative, immunologic, and inherited diseases. Yet, the status remains in early development, and scientific, regulatory, and cost-effectiveness issues impose considerable hurdles toward marketing authorization, technology adoption, and patient accessibility. In this context, although regenerative dentistry has achieved breakthrough innovations in TE of several dental/oral tissues in preclinical models, it has hardly harnessed research progress to integrate innovative regenerative treatments into clinical practice. Conclusion: Global demographic changes, which demonstrate a steady increase of the aging population, highlight the societal need for the application of ATMP-based therapies in the treatment of noncommunicable diseases (NCDs). Although oral diseases, as an integral part of NCDs, are not life-threatening and largely preventable, they sustain high prevalence, with severe burden on economy and quality of life. In this perspective, the urgent request to ultimately translate draining research in dental TE conducted during the last decades into innovative treatments brought safely and cost-effectively into society at large still holds the stage. This review provides an overview of the regulatory, clinical, and commercial status of ATMP-based therapies in the European Union and worldwide and the hurdles to overcome for their broader application in regenerative dentistry. (J Endod 2020;46:S175–S188.)

KEY WORDS

Advanced therapy medicinal products; implementation science; regenerative dentistry; regulatory framework; tissue engineering; translational research

During the past years, advanced therapy medicinal products (ATMPs), consisting of somatic cell therapy medicinal products (SCTMPs), tissue-engineered products (TEPs), gene therapy medicinal products (GTMPs), and combined ATMPs, have been under active research in the European Union (EU) and worldwide. This has been the physical consequence of the rise in global share of severe, incurable diseases.
noncommunicable diseases (NCDs), such as Parkinson’s, Alzheimer’s, autoimmune, heart diseases, strokes, cancer, diabetes, chronic kidney failure, and osteoarthritis, just to mention a few. SCTMs and TEPs are defined as consisting of cells/tissues and cell/tissue-based TEPs, respectively, that have been subject to substantial manipulation or are not intended to be used for the same essential function(s) in the recipient and the donor. GTMPS include products containing recombinant nucleic acid of biological origin applied for regulating, repairing, replacing, adding, or deleting a genetic sequence for therapeutic, prophylactic, or diagnostic purposes. Dental diseases, including dental caries, endodontic infection, periodontal disease, tooth loss, as well as oral diseases such as oral cancer, are an integral part of the NCD group, sharing common characteristics in being chronic and strongly socially patterned and disproportionately affecting lower- and middle-income countries. They also share common risk factors with other NCDs, such as sugar, smoke, and/or alcohol consumption. Although dental/oral diseases are in their majority not life-threatening and largely preventable, except for oral cancer, they are characterized by very high prevalence, affecting more than 3.5 billion people around the world. The latter is associated with a significant burden on the economy and a severe impact on quality of life (QoL). The direct and indirect global economic impact of oral conditions may amount to more than US$442 billion, and these estimates will keep rising with increasing disability-adjusted life year estimates. Oral infections may also act as risk/aggravating factors for systemic diseases such as cardiovascular diseases or metabolic syndrome. Current treatment modalities, including tooth fillings, endodontic treatment, prosthetic rehabilitation, and implant-based tooth replacement, are subject to several biological and technical complications and adverse reactions, overall compromising their long-term therapeutic efficacy. In this respect, the urgent need to manage dental/oral diseases on a long-term basis has been described as a global health priority.

Tissue engineering (TE), focusing on the development of artificial organs, engineered tissues, and cell-based therapies, represents a promising innovative approach with the potential to overcome limitations encountered in current therapeutic methods. Until now, extensive research in dental TE has achieved breakthrough innovations in the regeneration of several dental/oral tissues in preclinical models that have been systematically reviewed. Briefly, several sources of adult dental tissue-derived mesenchymal stem cells (MSCs), such as dental pulp SCs from permanent (DPSCs), or deciduous (SHED) teeth, SCs from the apical papilla, dental follicle SCs, periodontal ligament SCs (PDLSCs), and orofacial bone marrow MSCs (BM-MSCs), among others, have been discovered and extensively studied regarding biological properties. It has been shown that different subsets of dental MSCs may be distinguished on the basis of the expression of surface markers and show variable potential to regenerate dental/oral tissues in vitro and in vivo. In contrast to other SC sources representing the gold standard in regenerative medicine, such as the bone marrow, and the adipose tissue-derived MSCs, dental MSCs have been shown to possess functional peculiarities that render them as the cell source of choice for dental TE.

TE of various dental tissues, through cell-based or cell-free approaches, has been accomplished. Sophisticated in vitro and in vivo systems have been developed. Bioengineering of various constituents of dental tissues, such as dentin, pulp, enamel, periodontal tissues, or alveolar bone, has been achieved by the combination of scaffolds, SCs, and growth factors. Of major interest is the regeneration of neovascularized dental pulp and “bio-roots” or even fully functional teeth in animal models. Extensive research on biomaterials (including natural polymers, proteins/peptides, synthetically engineered polymeric and ceramic biomaterials, etc) used as scaffolds in conjunction with microenvironmental modulation via stimul-responsive components represents the pillars of the above-mentioned translational research achievements. In addition to dental applications, research has been conducted on the application of dental MSC secretome in the treatment of other medical conditions such as cardiovascular diseases, diabetes mellitus, hepatic regeneration, and skin injuries because of its enhanced antiapoptotic, angiogenic, neurite outgrowth, and immunomodulatory properties, as compared with other non-dental secretomes. In addition, the application of extracellular vesicles as cell-free therapy has also emerged as a promising therapeutic strategy.

Despite these achievements, translation into clinical applications in real life remains disproportionally low. It has been reported that it takes, on average, 17 years to integrate 14% of original research into clinical practice. The most probable reason for this inefficient outcome derives from difficulty in obtaining sufficient preclinical and clinical safety and efficacy data to support further investment into the new ATMPs. In addition, regulatory hurdles requiring extensive communication with the national and international authorities and the high risk of capital investments in innovative solutions found at the early stage of research severely restrict integration of novel ATMP-based therapies into the clinic.

Several recent reviews provide summaries of ATMP-based therapies in Europe and worldwide. This review builds on this prior work by focusing on the current landscape of regulatory, clinical, and commercial status of ATMP-based therapies, with particular emphasis on the challenges toward implementing innovative and efficient solutions in regenerative dentistry.

**DISCUSSION**

**Regulatory, Clinical, and Commercial Landscape of ATMP-Based Treatments**

ATMPs represent complex biomedicines containing living cells or subcellular fractions with biological functions, which require high-level scientific evaluation of their safety and efficacy before proceeding to commercialization, technology adoption, and clinical application. A significant effort has been attempted by stakeholders in the EU and worldwide during the past few years to overcome the “Death Valley” of clinical translation and to develop multilevel implementation plans to accelerate patient accessibility in ATMP-based treatments; their results, however, are yet to be seen. ATMPs are regulated in the EU by the Directives 1394/2007 and 2009/120/EC amending the directive 2001/83/EC and controlled by the Committee for Advanced Therapies and the Committee for Medicinal Products for Human Use of the European Medicines Agency (EMA). The latter is equivalent to the Food and Drug Administration (FDA) in the United States. According to these regulations, the main requirement for the production of ATMPs for human use is the accreditation, designation, authorization, or licensing of tissue establishments and cell preparation processes. These include the development of standard operating procedures, training and reference manuals, reporting forms, donor records, and information on the final destination of tissues or cells. Cell and tissue handling and manipulation are performed under Good Manufacturing Practice (GMP) conditions, regulated by the directive 2003/2006/EC, which has become an integral part of the legislative redlines. GMP secures that ATMPs...
meet the quality standards defined by their intended use and comply with the marketing authorization (MA). It also allows traceability of the materials and final products, emergency unblinding of the studies, and monitoring deviations from the internally determined quality standards.

Clinical trials for ATMPs, as for all other investigational medicinal products (IMPs), were initially regulated by the Directive 2001/20/EC66, which has been in force since 2004 and introduced Good Clinical Practice standards during conduction of clinical trials on ATMPs for human applications. Nevertheless, its legal content had to be translated into national legislation, leading to considerable variability in clinical trial approval, national specificities, and timelines. Recently, incorporation of the regulation 536/2014 on clinical trials65 that is pending to come in force is expected to lead to a more harmonized and expeditious process for clinical trial approval.

Similar regulatory frameworks, but also differences, are encountered in the US FDA. In legislative terms, advanced therapies encompass cellular and gene therapy products (CGTs). They should not be confused with other legislative categories of products called “human cells, tissues, and cellular and tissue-based products”, which are not considered biological products. A program called the Regenerative Medicine Advanced Therapy has also been enforced in 2016 through the 21st Century Cures Act as part of the US advance therapy classification. CGTs are regulated by the Center for Biologics Evaluation and Research under the authority of Section 351 of the Public Health Service Act, as well as Title 21 of the Code of Federal Regulations Part 127167. In both the EU and the US, substantial manipulation that alters their biological characteristics is a prerequisite to classifying a cell- or a tissue-based product as an advanced therapy67.

One of the main differences between the EU and the US is that the FDA oversees clinical trials, whereas the EMA does not. The FDA’s primary concern focuses on product safety and human subject protection, whereas that of EMA lies in its current focus in facilitating the development of innovative therapies to address unmet medical needs. In other regulatory bodies worldwide, there are no uniform safety standards for the regulation of ATMPs. Toward harmonization of SC research translation policies into clinical applications, the International Society for Stem Cell Research published guidelines based on recommendations by researchers, clinicians, and stakeholders from 13 countries57.

Most surprisingly, although more than 500 clinical trials using ATMPs have been running in EU58 and more than 900 worldwide59, only 12 ATMPs have been finally approved since the enforcement of the 1394/2007 Directive, and another 6 are close to MA; of those 4 licensed ATMPs (Provenge, MACI, Glybera, and ChondroCelect) have been withdrawn from the market, primarily because of extremely high costs leading to commercial failures5. All 12 ATMPs with past/present MA in the EU came to light to address serious medical conditions with insufficient available treatments, including inherited diseases (Glybera, Strimvelis), cancer (Irymyic, Zalmoxis), cancer immunotherapy (Yescarta, Kinnirah, Provenge), tissue regeneration (eg, loss of sight, Holocar), immune diseases (Alofaseil), and cartilage defects (ChondroClect, MACI, Spherox).

This vast discrepancy between the number of innovative ideas and translation to actual treatment modalities is attributed to both scientific and regulatory challenges, stemming from key differences between ATMPs and other IMPS. In specific, ATMP-based therapies are genuinely personalized and, therefore, not produced on a routine basis, a fact that launches the production costs and significantly complicates the manufacturing process60. Evaluation of their safety and efficacy can also be challenging. Scientific challenges include a lack of relevant animal models to demonstrate proof-of-principle of novel products before initiation of clinical trials, difficulties in monitoring their efficacy and in vivo distribution, and to define the effective doses61. Assessment of cost-effectiveness and risk assessments represent even more insurmountable difficulties toward product licensing62.

Several compromises have been adopted by research groups to facilitate the implementation of clinical trials on ATMPs. These include the adoption of suboptimal study designs, such as short-term, early phase, single-arm, or single-center clinical trials62, as well as the use of surrogate endpoints, for example, laboratory measurements rather than clinical parameters61. The aim is to establish paradigm shifts to accelerate patient access to novel regenerative therapies, even if on the basis of lower levels of evidence. Hospital exemption represents a common outlet to overcome standard licensing procedures from EMA. It refers to treatments prepared under the professional responsibility of a medical practitioner on a non-routine basis and according to specific quality standards that are applied for individual patients64. Taking advantage of this shortcut, 32 ATMPs are available in individual EU countries, in addition to the 12 having central MA. Nevertheless, concerns are emerging from the extensive use of hospital exemption at national levels, because it may restrain the submission of MA applications to the EMA. Although all the above-mentioned “short cuts” may be related to biased or imprecise results, they represent a primary source of prevailing paradigms paving the way for further experimental research and translation65,66.

All these challenges hampering ATMP development have recently been the subject of discussion during a multi-stakeholder meeting of experts and regulators released by EMA on 2016, almost 10 years after the enforcement of the 1394/2007 regulation on ATMPs5. The main conclusion of this meeting was that there is an urgent need to nurture a regulatory environment that encourages innovation, safeguards public health, and facilitates timely patient access to new therapies. Other strategies, including community-based research based on social data, such as those concerning demographic changes and a tremendous shift in the share of NCDs in the general population, coupled with other systematic interventions to adopt and infiltrate evidence-based research in education and day-to-day health care, represent measures to achieve a broader diffusion to the patients. Nevertheless, only time will tell as to which degree ATMP-based therapies will fulfill their promise of treating a wide range of NCDs plaguing the modern world. On the other side of the coin, serious efforts to establish a more flexible regulatory framework are taking place in global scenery of unlimited application of SCs by a respectable number of unauthorized clinics selling hope “on culture dishes.”

**Status of ATMP-Based Treatments in Regenerative Dentistry**

Priorities in healthcare policies are configured not only by the self-evident need to manage severe, highly debilitating conditions but also the global demographic changes leading to an expanding aging population, which in turn increases the need for new therapies and resources to treat a wide range of NCDs and the associated social and economic consequences52. Dental and oral diseases, leading to tooth loss and edentulism, are part of the NCD heatmap and are characterized by high prevalence and severe contribution to the decline of QoL because of restricted chewing function, impaired esthetics, and overall patient disability.

Current treatment modalities in endodontics, periodontics, restorative dentistry, prosthodontics, implantology, oral surgery, and other dental fields are characterized by several limitations in terms of...
reparative potential, morbidity, and stability over time. This is associated with substantial economic and societal shortcomings. A typical example would be early tooth loss in young individuals because of congenital tooth absence, dental trauma, or failure to provide long-term treatment to immature teeth with pulpal necrosis and the subsequent need for implant-based tooth replacement. The latter is associated with several functional and esthetic challenges encountered during construction, long-term maintenance, and replacement of the implant and/or restoration when they fail after a certain number of years. In this context, TE has been the focus of attention, and novel cell-based therapies have been added to the armamentarium of regenerative dental treatments\textsuperscript{13}. For example, it is envisioned that transplantation of stem cells and/or the application of bioactive signaling molecules may allow a more physiological regeneration of the dentin-pulp complex, the surrounding alveolar bone, and, ultimately, TE of a whole “biroot” may be a clinical reality\textsuperscript{68}.

The dental community has now realized the urgent need to translate current research findings into novel ATMP-based therapies. Except for the regulatory and commercial challenges applicable to other medical fields, there are several special scientific issues that need to be solved\textsuperscript{15}. In particular, development of standard operating procedures for the clinical grade, serum/xeno free expansion of oral stem cells to the desired numbers (upstream process)\textsuperscript{19}, maintenance of stemness vs minimization of senescence during expansion culture, GMP-grade selection (via fluorescent- or magnetic-activated cell sorting), transplantation of the most effective stem cell populations (downstream process), selection of the appropriate scaffolding materials, and microenvironmental modulation are among the most cutting-edge scientific issues to be addressed. Most importantly, collection of safety (through passing all quality controls\textsuperscript{70} and efficacy preclinical and proof-of-principle data to provide an at least acceptable level of evidence represents the main bottleneck toward broad clinical application.

Until now, several clinical studies have been published using MSCs for the regeneration of various oral tissues. Most of these studies were targeting orofacial bone regeneration, including regeneration of large-size (cleft palate, alveolar ridge augmentation, maxillary replacement, mandibular fracture replacement, sinus lift augmentation, and osteoradionecrosis cases) and small-size bone defects (eg, post-extraction sockets). These studies mainly comprised case reports or case series and few randomized controlled clinical trials (RCTs) and have been systematically reviewed by several authors\textsuperscript{34,71-73}. In the majority of these studies, BMMSCs and to a lesser extent other MSC types, such as periodontium-derived MSCs or adipose tissue-derived MSCs, have been used. It is also not clear whether the use of ex vivo expanded cells, either uncommitted or committed, is superior to whole tissue fractions, such as bone marrow aspirates—either whole or concentrated—, adipose stromal vascular fractions, or tissue micrographs in terms of bone regeneration\textsuperscript{74}. The latter has the advantage of avoiding the ex vivo clinical-grade expansion of oral stem cells, which is accounted as “substantial manipulation” and directs to the ATMP regulation pathways. It can be concluded from these studies that cell therapy is strongly indicated in cases of large defect sizes, such as alveolar cleft and trauma defects\textsuperscript{75}, severely atrophied mandibular bone\textsuperscript{76}, or mandibular fractures\textsuperscript{77}, however needing further RCTs to determine their cost-effectiveness for final decision making.

Very few clinical trials have been published on periodontal tissue reconstruction and have been systematically reviewed\textsuperscript{76,77}. Among these, only 3 RCTs\textsuperscript{78-80} and 1 phase I/II clinical trial\textsuperscript{81} provide higher levels of evidence, Chen et al\textsuperscript{79} applied PDLSC sheets in combination with bovine bone mineral (Biooss Biomaterials, Wolhusen, Switzerland) to treat intrabony defects (n = 21), while the lesions of the control group (n = 20) received Bio-oss alone. The cells were expanded ex vivo for approximately 30 days and passed all quality controls. The authors concluded that the proposed method was safe, although its superiority regarding clinical and radiographic parameters could not be proven. Ferrarotti et al\textsuperscript{80} applied DPSC-rich micrografts seeded onto collagen sponges to treat intrabony periodontal defects (n = 29), while the lesions of the control group (n = 20) received the collagen sponges alone. No cell expansion was performed in this study, because the pulp of the donor’s teeth was mechanically dissociated and immediately used; therefore, the proposed protocol cannot be considered as ATMP-based, but rather a cell-based treatment. Results favored the cell-based approach in terms of improvement of all clinical and radiographic parameters. Last, Baba et al\textsuperscript{81} performed a phase I/II clinical study without a control group, treating 10 patients with autologous BMMSCs expanded with conventional, bovine serum–containing medium (ie, not clinical grade) and loaded with platelet-rich plasma in a woven-fabric composite scaffold to treat intrabony defects. The method was safe and effective by improving all clinical parameters, although no further comparisons could be possible. Overall it can be concluded that low-quality evidence suggests that MSC-based therapy may have a small impact on periodontal regeneration. Still, it has to be further validated by multicenter randomized controlled studies with an increased sample size. Further endeavors include the determination of the optimal cell dosages and the more suitable scaffolding materials to address more challenging clinical scenarios, such as “hopeless” teeth with deep periodontal or combined periodontal/endodontic lesions.

Very few clinical trials have been published on pulp regeneration\textsuperscript{82-85}. Nakashima et al\textsuperscript{86} published studies on the potential of mobilized DPSCs to regenerate pulp in dog pulpectomized teeth, and on this basis, they have initiated a clinical trial, making a reality the standardization and establishment of regulatory guidelines for SC therapy in clinical endodontics. Xuan et al\textsuperscript{87} performed a well-designed RCT applying autologous deciduous teeth MSCs in the form of cell aggregates (ie, scaffold-free approach) in young patients (n = 26) with pulp necrosis after traumatic dental injuries, while the control group (n = 10) received conventional apexification treatment. The study was supported by extensive in vitro and in vivo (small- and large-animal models) preclinical documentation. The study provided auspicious results on the safety and efficacy of this treatment in the regeneration of three-dimensional pulp tissue equipped with blood vessels and sensory nerves, in addition to successful apexification in the experimental as compared with the control teeth. It should be mentioned that although the authors supported cell expansion to take place under current GMP conditions, conventional research-grade media and supplements have been used; nevertheless, all patients passed the safety evaluation assessments. In another well-designed RCT by Brizuela et al\textsuperscript{88} they applied umbilical cord–derived MSCs encapsulated in a plasma-derived biomaterial for regenerative endodontic procedures (REPs) (n = 18), while the control group (n = 18) received conventional root canal treatment. The results proved the safety of the REP method, while both groups showed 100% efficacy at 12 months, defined as tooth remaining in the mouth with no percussion pain and an apical bone lesion of equal size, decrease, or no more than a 0.1-mm increase. Nevertheless, the REP group showed statistically significant improvement in all sensitivity tests, compared with the control. Overall, this very important study validates this ATMP-based...
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<tr>
<td>Chronic periodontitis</td>
<td>Periodontal regeneration of chronic periodontal disease patients receiving stem cells injection therapy</td>
<td>Allogeneic human DPSCs</td>
<td>Local injection at the periodontal defects</td>
<td>Unknown</td>
<td>Phase 1/2, n = 40</td>
<td>Improvement of baseline alveolar bone volume and clinical parameters, including probing depth, clinical attachment level, Quigley-Hein plaque index, bleeding on probing</td>
<td>No results posted</td>
<td>NCT02523651</td>
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<td>Chronic periodontitis</td>
<td>Gingiva mesenchymal stem cells treatment of chronic periodontitis</td>
<td>GMSCs</td>
<td>GMSCs seeded into collagen scaffolds are applied at the periodontal defects</td>
<td>Unknown</td>
<td>Phase 1/2, n = 30</td>
<td>Increase in height of alveolar bone examined by CBCT. Probing pocket depth, attachment level, gingival index, tooth mobility degree</td>
<td>No results posted</td>
<td>NCT03137979</td>
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<td>Chronic periodontitis</td>
<td>Periodontal ligament stem cell implantation in the treatment of periodontitis</td>
<td>PDLSCs</td>
<td>Application of cell sheet pellets and cell sheet fragment into the defects</td>
<td>Unknown</td>
<td>Phase 1/2, n = 80</td>
<td>Bone loss, plaque index, probing depth, attachment loss</td>
<td>No results posted</td>
<td>NCT01082822</td>
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<td>Chronic periodontitis</td>
<td>Clinical trials of regeneration for periodontal tissue</td>
<td>BMMSCs</td>
<td>Injection in the form of a gel of mixture of ex vivo cultured MSCs, ex vivo cultured osteoblast-like cells differentiated from MSCs and a scaffold (consisting of platelet-rich plasma, human thrombin, and calcium chloride)</td>
<td>Completed</td>
<td>Phase 1/2, n = 10</td>
<td>Alveolar bone defect filling, tooth mobility</td>
<td>No results posted (Note: published by Baba et al, reference81)</td>
<td>NCT00221130</td>
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<td>Chronic periodontitis</td>
<td>Periodontal regeneration using dental pulp stem cells</td>
<td>DPSCs</td>
<td>Application of human micrografs containing DPSCs in the intrabony defects</td>
<td>Completed</td>
<td>N/A, n = 29</td>
<td>Radiographic bone fill and clinical measurements</td>
<td>No results posted (Note: published by Ferraroti et al, reference80)</td>
<td>NCT03386877</td>
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<td>Chronic periodontitis</td>
<td>Autologous alveolar bone marrow mesenchymal stem cells for the reconstruction of infrabony periodontal defects</td>
<td>BMMSCs</td>
<td>Application of a biocomplex comprising human BMMSCs, fibrin glue, and a collagen fleece in the infrabony defects</td>
<td>Completed</td>
<td>Phase 1/2, n = 30</td>
<td>Radiographic bone fill and clinical measurements</td>
<td>No results posted (Note: under publication by Apatzidou D, Bakopoulou A, et al)</td>
<td>NCT02449005</td>
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<td>Chronic periodontitis</td>
<td>Periodontal tissue regeneration using autologous periodontal ligament stem cells</td>
<td>PDLSCs</td>
<td>No further information posted</td>
<td>Unknown</td>
<td>Phase 1, n = 35</td>
<td>Radiographic bone fill and clinical measurements</td>
<td>Results posted but not publicly available</td>
<td>NCT01357785</td>
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<td>Chronic periodontitis</td>
<td>Regenerative potential of cultured gingival fibroblast-mesenchymal stem cells in treatment of periodontitis</td>
<td>Gingival mesenchymal stem cells (GMSCs)</td>
<td>Application of a mixture of gingival fibroblasts and GMSCs carried on a vehicle of ß-TCP and covered by resorbable collagen membrane</td>
<td>Completed</td>
<td>N/A, n = 20</td>
<td>Bone gain in periodontal defects at 6 months postoperatively assessed radiographically</td>
<td>No results posted</td>
<td>NCT03638154</td>
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<td>Dental pulp necrosis</td>
<td>Revitalization of immature permanent teeth with necrotic pulps using SHED cells</td>
<td>SHED</td>
<td>Application of scaffold-free SHED-derived pellet</td>
<td>Unknown</td>
<td>N/A, n = 80</td>
<td>Pulp status evaluated by dental pulp vitality tester; pulp revascularization examined by laser Doppler flowmeter and index of clinical examination, degree of apical closure, rate of increase in root length change, root canal wall thickness</td>
<td>No results posted (Note: published by Xuan et al, reference[82])</td>
<td>NCT01814436</td>
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<td>Irreversible pulp inflammation or dental trauma</td>
<td>Feasibility of the preparation of an ATMP for dental pulp regeneration</td>
<td>DPSCs</td>
<td>No information posted</td>
<td>Completed</td>
<td>N/A, n = 30</td>
<td>No information posted</td>
<td>No results posted</td>
<td>NCT02842515</td>
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<td>Periapical periodontitis</td>
<td>Encapsulated mesenchymal</td>
<td>Application of umbilical cord-</td>
<td>Completed</td>
<td>N/A, n = 38</td>
<td>Number of participants</td>
<td>Results proved the safety of the REP</td>
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<tr>
<td>Improvement of implant osseointegration</td>
<td>Effect on allogenic mesenchymal stem cells on osseointegration of dental implants</td>
<td>Allogeneic human DPSCs</td>
<td>Implant is dipped in stem cell solution for 3 minutes so that the cells adhere to the titanium implant surface before placement at the osteotomy site</td>
<td>Unknown</td>
<td>Phase 1, n = 10</td>
<td>Evaluation of primary and secondary stability is measured by using resonance frequency analysis</td>
<td>No results posted</td>
<td>NCT02731586</td>
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<tr>
<td>Alveolar bone preservation around dental implants</td>
<td>Dental implant placement in adjunction with autologous alveolar bone-marrow derived mesenchymal stem cells (aBMMSCs)</td>
<td>BMMSCs</td>
<td>Application of a biocomplex comprising human BMMSCs, fibrin glue, and a collagen fleece over the implant during placement</td>
<td>Completed</td>
<td>Phase 1/2, n = 20</td>
<td>Reduction in marginal bone levels from baseline (implant placement) to 4 months (implant exposure), intrasurgical clinical data, radiographic changes in marginal bone levels, reduction in thickness of buccal/lingual bone, changes in alveolar mucosa, and width of keratinized mucosa</td>
<td>No results posted</td>
<td>NCT03070275</td>
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<td>Jaw atrophy</td>
<td>Reconstruction of jaw bone using MSCs</td>
<td>BMMSCs</td>
<td>Augmentation of atrophied alveolar ridge BMMSCs and bis calcium phosphate</td>
<td>Completed</td>
<td>Phase 1, n = 13</td>
<td>Amount of newly formed bone at 4–6 months after augmentation assessed by CBCT</td>
<td>No results posted</td>
<td>NCT02751125</td>
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<tr>
<td>Alveolar bone TE for cleft lip and palate patients</td>
<td>Bone tissue engineering with dental pulp stem cells for alveolar cleft repair</td>
<td>Deciduous teeth stem cells</td>
<td>Association of MSCs with hydroxyapatite/collagen scaffolds and filling of defects</td>
<td>Recruiting</td>
<td>Phase 3, n = 62</td>
<td>Alveolar bone filling rate at 12 months postoperatively</td>
<td>No results posted</td>
<td>NCT03766217</td>
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<tr>
<td>Alveolar bone TE for cleft lip and palate patients</td>
<td>Use of MSCs for alveolar bone tissue engineering for cleft lip and palate patients</td>
<td>Deciduous teeth stem cells</td>
<td>Application of MSCs inside a collagen and hydroxyapatite biomaterial (Geistlich Bio-Oss) into the defect (secondary alveolar graft after completion of orthodontic treatment)</td>
<td>Completed</td>
<td>N/A, n = 5</td>
<td>Amount and quality of regenerated bones (CT scans)</td>
<td>In all 5 patients satisfactory bone formation closing the alveolar cleft observed after 6 months</td>
<td>NCT01932164</td>
</tr>
<tr>
<td>Alveolar bone TE for cleft lip and palate patients</td>
<td>Concomitant use of buccal fat pad derived cells (BFPSCs) and autogenous bone in alveolar cleft osteoplasty</td>
<td>BFPSCs</td>
<td>BFPSCs cultured on natural bovine bone mineral were put over anterior iliac crest spongy bone to fill defects and covered with a collagen membrane (secondary alveolar graft after completion of orthodontic treatment)</td>
<td>Completed</td>
<td>Phase 1, n = 10</td>
<td>Change in bone volume 6 months postoperatively assessed by CBCT</td>
<td>No results posted</td>
<td>NCT02859025</td>
</tr>
</tbody>
</table>

(continued on next page)
<table>
<thead>
<tr>
<th>Indication/disease</th>
<th>Title</th>
<th>Type of cells</th>
<th>Type of ATMP-based treatment in experimental group(s)</th>
<th>Status</th>
<th>Phase/no. of subjects</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Clinicaltrials.gov identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus lift augmentation</td>
<td>Effect of BFPSCs in maxillary sinus augmentation</td>
<td>BFPSCs</td>
<td>Application of BFPSCs loaded on freeze-dried bone allograft with platelet-rich fibrin for sinus augmentation</td>
<td>Unknown</td>
<td>Phase 1, n = 20</td>
<td>Amount of regenerated bone assessed by CBCT</td>
<td>No results posted</td>
<td>NCT02745379</td>
</tr>
<tr>
<td>Posterior mandible reconstruction</td>
<td>BFPSCs with cortical tenting in posterior mandible reconstruction</td>
<td>BFPSCs</td>
<td>Application of BFPSCs loaded on freeze-dried bone allograft (with platelet-rich fibrin at the recipient site)</td>
<td>Unknown</td>
<td>Phase 1, n = 20</td>
<td>Amount of regenerated bone assessed by CBCT and histomorphometric analysis</td>
<td>No results posted</td>
<td>NCT02745366</td>
</tr>
<tr>
<td>Sinus lift augmentation</td>
<td>Effectiveness and safety of method of maxilla alveolar process reconstruction using synthetic tricalcium phosphate and autologous MMSCs</td>
<td>Oral mucosa MSCs</td>
<td>Oral mucosa MSCs mixed with synthetic tricalcium phosphate are applied for sinus augmentation</td>
<td>Unknown</td>
<td>Phase 1/2, n = 12</td>
<td>Amount of regenerated bone assessed by CBCT and histomorphometric analysis</td>
<td>No results posted</td>
<td>NCT02209311</td>
</tr>
</tbody>
</table>

β-TCP, β-tricalcium phosphate; CBCT, cone-beam computed tomography.
innovative approach in the regenerative treatment of dental pulp and periapical pathology.

It should also be mentioned that a reason for the limited number of SC-based studies for pulp regeneration is that the predominating attitude in regenerative endodontics is based on cell-free approaches, which encompasses either induction of the revascularization through the recruitment of endogenous stem cells from the periapical region or the injection of bioactive scaffolds that eventually undergo cell-mediated degradation to be replaced with natural extracellular matrix. Both approaches may be accompanied by the application of potent chemoattractants and growth factors to induce cell migration, proliferation, and differentiation. All these methods have been described as being safer, more practical, feasible, and affordable for pulp regeneration, compared with the cell-based scenario. Nevertheless, one caveat of the cell-free approaches is the failure for achieving pulp-like or dentin-like regeneration, but rather periodontal tissue ingrowth into canal space.

Apart from the published studies, a considerable number of studies targeting TE of various dental tissues are currently underway or in phase of completion, as shown by data obtained by the clinicaltrials.gov database, and are analytically described in Table 1.

CONCLUSION

ATMP-based therapies are expected to substantially change disease outcomes in millions of patients suffering from a wide variety of NCDs worldwide and therefore improve patients’ QoLs in a steadily “aging world”. Clinical translation into advanced therapies of innovative ideas is challenged not only by scientific hurdles but also by a lack of expertise in regulatory science and cost-effective commercialization of the final products. It is crucial to identify the unmet needs and achieve a collaborative “fast-track” between academia, industry, stakeholders, and regulatory authorities to improve product designs and usability, increase chances of success, and ultimately accelerate translation into medical technologies. According to Caplan et al, Regulation, Reimbursement, and Realization represent the 3 Rs for getting cell therapies efficiently and safely to patients. In the field of regenerative dentistry, oral health applications have been particularly hampered by low prioritization, mainly because they are dealing with non-life-threatening conditions. Because of the high prevalence and significant contribution of oral diseases on overall disability, deterioration of QoL, and burdening the health economics, there is an urgent need for supporting research on ATMP-based oral applications, through the initiation of well-designed RCTs, to provide higher levels of evidence on the regenerative treatment of various oral tissues. This will shed more light on the safety and efficacy of these innovative treatments compared with conventional modalities and foster efforts to surmount any problems bringing these transformative therapies safely to patients.

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REFERENCES


59. Seimetz D. What can we learn from case studies to address development and approval challenges of ATMPs? Hum Gene Ther 2017;28:A61–2.


