Osteoradionecrosis of the Jaw–Thinking Outside the Box, a Review of Emerging Treatment Paradigms

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Abstract: Osteoradionecrosis (ORN) of the jaw occurs due to the damaging effects of ionizing radiation used in the treatment of head and neck cancer, including oral cavity or oropharyngeal, nasopharyngeal, and salivary gland sites. Medical treatments for ORN have limited effectiveness in advanced cases, often necessitating resection of affected bone with microvascular reconstruction using a bone-containing free flap in advanced cases. Surgical innovations in minimally invasive free fascial and periosteal flaps have shown promise in restoring blood supply and halting disease progression, although they are not universally successful. In addition, novel cell-mediated regenerative treatments for osteoradionecrosis, including the use of adipose-derived and bone marrow-derived stem cells in craniomaxillofacial defects, have also demonstrated potential. The management of intermediate ORN remains a subject of debate, leading to a review of novel approaches to address this challenging condition. This review evaluates the efficacy of a range of treatment options, including new cell-based treatments for osteoradionecrosis (ORN) by analyzing literature from Medline, PubMed, and Embase databases using search terms such as â€œosteoradionecrosis,â€ â€œstem cells,â€ â€œtherapy,â€ â€œradiation,â€ and â€œreconstructive surgery.â€ Relevant papers for this review were triaged by abstract and title, categorized by topic or procedure, and subsequently read and summarized. Experimental studies of cell-based treatments for ORN in human patients and animal models show promise and support further exploration of this emerging treatment strategy.

Key Words: Osteoradionecrosis of the jaw, radiation, reconstructive surgery, stem cell therapy

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Osteoradionecrosis of the jaw (ORN) is caused by the damaging effects of ionizing radiation used to treat cancer of the oral cavity or oropharynx. ORN typically develops months to years following treatment of cancer of the upper aerodigestive tract, with the mandible the most frequently affected subsite of the oral cavity. It is estimated that 3% to 5% of patients who undergo radiation therapy (XRT) for treatment of head and neck cancer develop ORN.[1]

ORN can be a debilitating clinical condition with a significant impact on quality of life. Medical treatment of ORN has been met with limited success and advanced stage ORN typically requires resection of involved bone with vascularized free tissue reconstruction.[2,3] While surgical management of ORN is technically challenging and can involve notable morbidity with an additional donor site, a bony free flap is the gold standard treatment and is the only option that allows for dental rehabilitation with implants.[4–6] Advances in animal modeling of ORN, coupled with innovations in stem cell therapies and tissue engineering have set the stage for application of novel cell-mediated regenerative treatments for ORN. Here, we will review the theory and rationale behind current treatments for ORN, as well as the recently developed animal models that will potentially enable innovation and preclinical trials of novel treatments for ORN, including cell-based therapies.

MATERIALS AND METHODS

In this systematic review, we assessed staging systems, pathogenesis theories, and therapeutic approaches for osteoradionecrosis (ORN). Articles were retrieved from PubMed, MEDLINE, and the Cochrane Library, using predefined inclusion criteria targeting studies on ORN staging classifications, pathogenesis, risk factors, and treatment interventions. Extracted data were organized to evaluate ORN pathogenesis theories and various treatments, including pharmacologic, surgical, and cell-based interventions. Searches were performed employing a combination of keywords, including "osteoradionecrosis," "stem cells," "therapy," "radiation," and "reconstructive surgery," in various permutations to capture relevant studies. This study is classified as a review article and received an exemption from the local institutional review board.

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thereby not requiring formal ethical approval for the analysis of published data.

Defining the Problem

Defining ORN and establishing a uniformly adopted staging system has remained an ongoing clinical challenge.[7] Classically ORN has been defined as devitalized and nonhealing necrotic bone that is exposed through overlying skin or mucosa following radiation therapy persisting 3 months or longer.[8] The requirement for bone exposure has recently been called into question, and it is now recognized that cases of ORN can occur in which bone is not exposed.[9] Classification schemes developed by Marx, Epstein, and Notani have been utilized with varying levels of success.[8,10,11] A uniformly adopted system has eluded description, though the model proposed by Epstein et al[10] is the most widely adopted. Alternative staging systems have been reviewed recently.[12]

Theories of Pathogenesis

Since Ewing 1926 description of â€œradiation osteitis,â€ multiple theories have emerged regarding the pathogenesis of osteoradionecrosis (ORN), with early suggestions linking it to trauma and infection, though recent views consider bacteria a surface contaminant rather than a primary cause.[13,14] In the 1980s, Marx introduced a new theory attributing ORN to radiation-induced vascular injury, leading to hypoxia and chronic tissue breakdown, supported by Bras et al[15] findings of ischemia from obliterated mandibular arteries in irradiated specimens.[16] Current concepts of the pathogenesis of ORN favor cellular and metabolic alterations that result in cell death and deregulation of collagen production that result in chronic nonhealing wounds. These theories are summarized below:

The Osteoclast Theory

Proposes that osteoclast damage from radiation, occurring before vascular injury, disrupts bone turnover and leads to ORN, drawing similarities to medication-related osteonecrosis of the jaw (MRONJ), where osteoclast inactivation is a key factor due to bisphosphonates and other medications binding to bone mineral and being internalized by osteoclasts.[17] The osteoclasts are inactivated and osteoclast-mediated bone resorption, an essential component of healthy bone turnover, is disrupted leading to risk of osteonecrosis.[14,18]

The Fibroatrophic Theory

Developed by Delanian and Lefaix,[19] it proposes that radiation depletes fibroblasts: the surviving cells have a reduced ability for collagen production, leading to dysregulated healing and tissue atrophy in ORN. The fibroatrophic theory describes 3 phases of ORN: an initial prefibrotic phase with acute inflammation and endothelial damage, an organizing phase with dysregulated fibroblast activity and extracellular matrix disorganization, and a late fibroatrophic phase characterized by tissue remodeling and fragile tissues prone to reactive inflammation.

The Endothelial Cell Theory

This theory suggests that radiation-induced endothelial injury and some medications generate free radicals and chemotactic factors, promoting an influx of inflammatory cells. These mediators release more free radicals and reactive oxygen species, causing further endothelial damage, microvascular thrombosis, and myofibroblast proliferation, ultimately leading to ORN.

Risk Factors for ORN

Though the exact pathophysiology underlying ORN remains elusive, clinical work has demonstrated a number of risk factors that are thought to play a role in the development of ORN. In the absence of curative therapy, mitigating risk is likely the most important factor in preventing the sequela of ORN. Risk factors that have been associated with the development of ORN include T stage and bone invasion of primary tumor, brachytherapy, dose of XRT >60 Gy, smoking history and smoking during treatment, poor oral hygiene, pre-existing periodontal disease, diabetes mellitus (DM) or immunocompromised history, prior mandibulotomy (?), and alcohol use.[20,21] Newer techniques of radiation, including the use of intensity modulated XRT are thought to be associated with decreased risk. The association of concurrent chemotherapy with XRT is controversial. Dental surgery, including extractions following therapy have been associated with the development of ORN.[20,22–25] Dental extraction may be necessary, and its link to ORN might stem from underlying infections and inflammation that stress alveolar bone repair, rather than just extraction trauma[25] Avoidable risk factors, such as pre-existing periodontal disease, should be managed before XRT to reduce necrosis risk. However, unavoidable factors like large tumors or XRT doses over 60 Gy require better preventive and therapeutic strategies for ORN. Figure 1 reviews intervention points before, during, and after XRT.

RESULTS

Medical Treatments

Therapeutic interventions for treating and preventing ORN are closely linked to the prevailing theories of its pathophysiological mechanisms at the time these interventions are developed.

Antibiotics

Initially, infection was thought to be crucial in the pathogenesis of ORN, but research has shown that microorganisms are likely just surface contaminants and do not significantly contribute to the disease's onset.[26] Antimicrobial therapy can be beneficial during symptom exacerbation or in cases of concomitant bone infections like osteomyelitis, using topical mouthwashes and/or systemic antibiotics. However, long-term antibiotics have not shown therapeutic benefits in ORN management;[8] while they may reduce secondary infections and symptoms, they can also promote antimicrobial resistance that requires attention to signs and symptoms of infection and antibiotic rotation. There is growing interest in researching the role of the oral microbiome in oral health and disease, particularly regarding the pathogenesis and progression of ORN.[25]

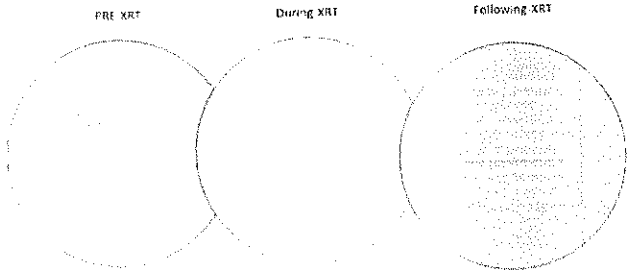

FIGURE 1. Points of intervention in the management of osteoradionecrosis. Opportunities to intervene at each point in treatment are outlined. EtOH indicates alcohol; HBO, hyperbaric oxygen treatment; IMRT, intensity modulated radiation therapy; XRT, radiation.

Hyperbaric Oxygen

Hyperbaric oxygen (HBO) was initially adopted for treating osteoradionecrosis (ORN) based on Marx RE's hypoxia-centric theory. Initially considered a key treatment for ORN,[8] HBO's benefits have since been questioned by further clinical research. These studies include a prematurely terminated multicenter, randomized, double-blind, placebo-controlled trial due to lack of benefit for HBO.[27] The discrepancy between early reports and later trials may be due to the stage of ORN treated,[9] with very early ORN potentially responding better to HBO. Current guidelines no longer recommend HBO for preventing or managing ORN due to lack of demonstrated benefit.[27] However, many clinicians use HBO before surgery for early-stage ORN, and evidence suggests it may improve microvascular reconstructive outcomes by reducing complications.[28]

Pentoxifylline and Alpha-tocopherol

Pentoxifylline, an antagonist to inflammatory mediators like TNFa, may improve microcirculation and is approved for intermittent claudication in Europe. Alpha-tocopherol (vitamin E) scavenges free radicals and protects cell membranes from lipid peroxidation.[29–33] Clodronate, a unique bisphosphonate, is believed to enhance bone formation and reduce fibroblast proliferation. Several studies have examined clodronate combined with pentoxifylline and tocopherol for ORN of the mandible and temporal bone.[34–36] In a systematic review of this data the percentage of a complete cure or clinical improvement is > 60% with the duration of response ranging from 6 to 13 months. The greatest rates of healing and clinical improvement are seen in mild and moderate stages of ORN. Further prospective clinical trials will be necessary to establish the efficacy of the combination of these agents as well as the optimal dose.

Teriparatide

Teriparatide, a recombinant human parathyroid hormone, is hypothesized to enhance osteoblastic activity through its anabolic effects.[37] An initial report on teriparatide use for managing medication-related osteonecrosis of the jaw (MRONJ) showed complete healing in all 6 patients within 2 months.[37] Furthermore, a study of 17 patients found that combining teriparatide with bone morphogenetic protein (BMP)-2 led to greater bone formation compared with using BMP alone or with control subjects.[37]

Amifostine

While amifostine was approved by the U.S. Food and Drug Administration for the prevention of xerostomia in head and neck cancer patients undergoing radiation therapy, pretreatment with amifostine in a murine model of irradiated pathologic fracture preserved osteocyte number and function to levels comparable to nonirradiated bone.[38] Furthermore, prophylactic amifostine significantly increased boney union rates to 57% to 100%, compared with 20% to 25% in irradiated controls, while also maintaining bone mineralization at nonirradiated levels 18 weeks postradiotherapy, with no significant differences in mineral density or mineral-to-collagen ratios between groups.[38]

Deferoxamine

Deferoxamine has been shown to enhance bone healing and increase vascularity at fracture sites, and in cases of irradiated fractured bone, its use significantly boosted bony union rates from 25% to 67% and improved local blood supply compared with the irradiated control.[38] Deferoamine demonstrated a bony union rate reaching 91%, compared with a low 20% in irradiated controls.[38] The 91% union rate demonstrated a significant improvement in biochemical strength and a 24% increase in bone healing over the 67% achieved with the standard deferozmine therapy.[38]

Photodynamic Therapy

Photodynamic therapy (PDT) involves using low-dose light treatments with an exogenous chromophore.[39] Unlike photobiomodulation, PDT generates higher levels of reactive oxygen species to destroy target cells, such as microbes, tumors, or endothelial cells.[39] In a patient with ORN, PDT administered twice weekly after dental surgery led to complete healing, with no recurrence observed at the 1-year follow-up.[39] Combined photobiomodulation (PBM) with methylene blue PDT has shown potential in enhancing osteoblast biological activity and cell proliferation, which hold significance in osteonecrosis management.[39] A preventive PDT protocol for patients at risk of MRONJ used 0.1% methylene blue during dental extraction, followed by weekly photobiomodulation until mucosal wound healing was complete.[39] Using this protocol, none of the 18 patients developed MRONJ after the extraction.[39]

Platelet Rich Fibrin

A few case reports suggest that platelet-rich fibrin (PRF) may be beneficial as an adjunct to surgical therapy for osteoradionecrosis (ORN), although no controlled studies have been conducted.[40] PRF's potential benefits in preventing and treating ORN are linked to its ability to promote wound healing, tissue regeneration, inflammation regulation, and revascularization.[40] Law et al[41] proposed using sequestrectomy with PRF and free fat grafts as an alternative to more invasive surgeries, while Baliga et al[42] recommended adding simvastatin to PRF for Stage 1 ORN. Maluf et al[43] reported promising results with PRF in advanced cases, potentially reducing the need for extensive surgeries. Chen and Chang[44] also supported the use of PRF's alongside sequestrectomy. However, no standardized treatment protocol has been established, and further clinical trials are needed.

Guidelines

The International Society of Oral Oncology-Multinational Association for Supportive Care in Cancer (ISOO-MASCC) and ASCO assembled a multidisciplinary Expert Panel to develop guidelines for the prevention, assessment, grading, and management of ORN of the mandible and maxilla in HNC patients previously treated with RT.[45] The panel indicated that patients receiving a radiation dose of 50 Gy or higher to the jaw should be considered at risk for developing ORN.[45] The recommended best practices for preventing ORN after radiation therapy include prescribing oral antibiotics before and after invasive dental procedures, such as extractions or implant placements, for patients at higher risk due to prior radiation involving the mandible and/or maxilla.[45] Recommendations for patients planned to receive dental surgery include pentoxifylline (400 mg twice daily) and tocopherol (1000 IU once daily) for at least 1 week before and 4 weeks after the procedure, continuing until the dental socket has healed.[45]

Nonsurgical management of ORN in cancer-free patients may include using pentoxifylline, particularly in combination with tocopherol, antibiotics, and prednisone, for mild to severe cases.[45] Furthermore, HBO therapy, when combined with surgical intervention, may benefit mild cases but can also be considered for moderate and severe cases,[45] although prospective study remains necessary.

Surgical management of ORN depends on the severity of the condition. For partial thickness cases (ClinRad stages I or II),

transoral minor interventions may effectively resolve the issue.[45] Small defects under 2.5 cm may heal spontaneously with local measures, whereas larger defects may require coverage with vascularized tissue.[45] In cases of full thickness ORN (ClinRad selected stages II and all stage III), segmental maxillectomy or mandibulectomy with free flap reconstruction is recommended.[45] When conservative treatments fail to control the disease in extensive partial thickness or full thickness ORN (ClinRad stages II or III), segmental resection is recommended. Maxillectomy defects that extend into the sinus (ClinRad stage III) can be reconstructed using myocutaneous or osteomyocutaneous flaps, which offer the added benefit of enabling dental implantation.[45] For patients who are not suitable candidates for microvascular surgery, obturation of the defect with a prosthetic appliance may be an option.[45] Mandibular continuity defects are best addressed with osteomyocutaneous free flap reconstruction.[45]

No recommendations were made for leukocyte-rich and platelet-rich fibrin or photobiomodulation in preventing ORN, and hyperbaric oxygen therapy was largely unsupported for its prevention and management due to limited evidence at that time[45]

Photobiomodulation

PBM involves using red or infrared light (630–950 nm) for biological effects, demonstrating analgesic, anti-inflammatory, and wound healing properties that may aid in treating ORN.[46,47] Mechanistically PBM is thought to mobilize stem cells and expand epithelial colony forming units in order to accelerate the repair of damaged tissue.[48,49] A meta-analysis of the effect of PBM on bone regeneration found that PBM impacts cellular and molecular pathways in bone regeneration, increasing osteocalcin, collagen RUNX-2, VEGF, bone morphogenic proteins, and COX-2.[50] In a recent review of the use of PBM in the treatment of medication-related osteonecrosis, there was an overall response rate of 55% versus 30% in controls.[51] Furthermore, rapid healing of necrotic mucosa in radiated oral sites has been described in case reports.[52] This evidence supports PBM as a promising treatment modality for ORN of the jaw, warranting further research to define its potential role and potential role in multimodality therapy. The World Association for Laser Therapy (WALT) recommends using an intraoral red (630–680 nm) or transcutaneous near-infrared (800–1100 nm) LED/laser device with a power density of 10 to 150 mW/cm^2, delivering 2 J/cm^2 per field, 3 to 4 times weekly for 4 to 6 weeks or until clinical improvement is noted.[53]

Surgical Treatment

Surgery is foundational in managing ORN. Conservative surgical options like sequestrectomy or debridement promote mucosal regeneration and potentially improve outcomes alongside medical treatments, though high-level evidence from controlled studies is lacking. Resection of affected bone with free flap reconstruction may provide definitive treatment for ORN unresponsive to conservative approaches. The involved bony area will certainly impact the dentition in and nearby the region. Without a bony free flap, the dental rehabilitation options are limited to a dental bridge or denture. While historically, free flaps were considered quite complicated, advances in microvascular surgical techniques have led to a more prominent role for free flap reconstructive surgery in the modern era. Bony free flaps, with greater versatility, improved outcomes, and allowance for dental implants, are currently considered the gold standard treatment for maxillofacial ORN.[45] In a few prospective trials on ORN management, Wang et al[54] found that resection with immediate fibula free flap reconstruction improved quality of life in 73% of patients and effectively managed pain. Multiple large retrospective studies support this data, showing that most patients experienced symptom resolution and improved quality of life, despite variability in complication rates.[55,56] In Figure 2, a case of severe recurrent ORN is reviewed that required resection of involved bone and microvascular reconstruction with a fibula free flap. Bony reconstruction with an osteomyocutaneous free flap is superior for enabling dental rehabilitation, however, in salvage cases or for patients with compromised medical status, a myocutaneous flap with a spanning reconstruction plate may be an alternative.

Preclinical Models

Developing an accurate preclinical animal model for ORN has been challenging but is essential for understanding the disease's pathogenesis. While rat models are commonly used, rabbit and swine models offer advantages due to their larger size and closer resemblance to human oral anatomy.

ORN has an enormous disadvantage in terms of a limited capacity to regenerate the defect given the lack of cellular elements, vascular and connective tissue elements and compromised healing environment. Improved animal models of ORN, closely aligned with human disease, have enabled mechanistic experiments and testing of cellular treatments. Various cell types are being studied for their roles in osteogenesis, which will be discussed in the following section.

Mesenchymal Stem Cells

Bone marrow-derived MSCs (BM-MSCs) are the most established cell source for clinical studies on bone tissue regeneration,[57] demonstrating regenerative potential in various craniofacial models due to their accessibility.[58] Xu et al[59] demonstrated that BM-MSCs are capable of inducing new bone formation and angiogenesis in a swine model of ORN. Likewise, in a rat model of ORN, Jin et al[60] demonstrated an increase in bone mineral density and bone volume when BM-MSCs were combined with BMP-2. In addition to animal model data, case series and reports suggest a potential role for mesenchymal stem cells in treating ORN, with successful treatments in 2 mandible cases using bone marrow concentrates and dental pulp. The authors propose that dental pulp-derived MSCs can differentiate into osteoblasts for bone production and can be

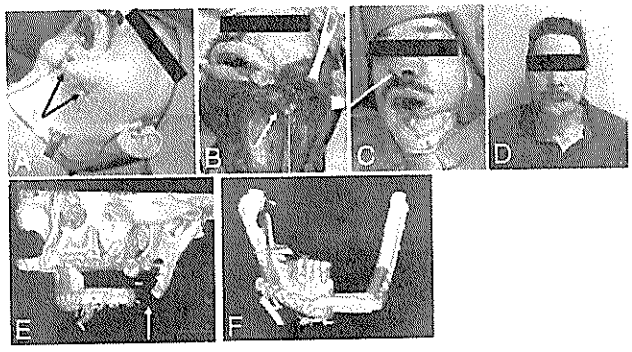

FIGURE 2. A clinical case of advanced osteoradionecrosis. This is a patient with a chronic draining orocutaneous fistula and a pathologic fracture involving previously placed mandibular hardware. (A) Preoperative photo, arrow depicts site of exposed hardware and orocutaneous fistula. (B) Intraoperative photo, arrow demonstrates exposure of the site of the pathologic fracture. (C, D) Immediate postoperative photo following reconstruction with a fibula free flap, and 3 weeks postoperative photo. (E, F) Three-dimensional reconstructed CT scans demonstrate the bone defect (arrow), and the restored bone continuity with a fibula free flap.

seeded onto scaffolds to repair bony defects. The authors demonstrate neoangiogenesis following stem cell therapy in ORN.[61] A report by Cella et al[62] demonstrated a case of bisphosphonate related osteonecrosis of the jaws that was successfully treated with an autologous transplant of BM-MSCs. In addition, Mendonca and Juiz-Lopez,[63] demonstrate impressive results using adult cultured stem and progenitor cells derived from iliac marrow aspirates to regenerate defects caused by terminal osteoradionecrosis. These authors show increased perfusion to graft sites using gadolinium-based MRI, indicating that reversing hypoperfusion can lead to lasting improvements in form and function.

Adipose Derived Stem Cells

The use of adipose-derived stem cells to treat radiation-damaged tissue has been explored for years, following evidence that these cells can generate osteoid.[64] Seminal experiments by Rigotti et al[65] demonstrated the use of lipoaspirates in enabling the regeneration of chest tissue that had previously been damaged by radiation. In one of the larger case series, ADSCs from the anterior abdominal wall were used to reconstruct craniomaxillofacial hard tissue defects in 13 patients, in conjunction with scaffolds and growth factors like BMP to enhance bone regeneration.[66] The report noted successful restoration of segmental mandibular defects of 6 to 10 cm, along with successful dental implantation. These results suggest that ADSCs, harvested with minimal morbidity, hold significant promise for craniofacial regeneration and potentially for treating ORN.

Induced Pluripotent Stem Cells

Induced pluripotent stem cells (iPSCs) have been proposed as a cell-based strategy to replace damaged or deficient tissues.[67] Recently, Levi et al[68] showed that iPSCs can be directed toward osteogenic differentiation in the presence of BMP-2 protein. The expansion of these cells to regenerate dental structures,[69] and to restore critical sized calvarial defects,[70] foster the hope that these cells would be helpful for the treatment of ORN. Alternatively, iPSCs could be used as a substrate to grow new bone following resection of diseased bone as an alternative to microvascular reconstructive surgery.

Dental Follicle Stem Cells

Dental Follicle Stem Cells (DFSCs) are recognized for their strong potential to differentiate into osteoblastic lineages, attributed to their neural crest origin, which is shared with craniofacial tissues.[71] This makes them valuable in maxillofacial tissue regeneration.[71] Research has shown that DFSCs express both early and late osteogenic markers, such as Runt-related transcription factor 2 (RunX2), osteopontin (OPN), and osteocalcin (OCN), and secrete bone morphogenetic protein-6 (BMP-6) to support osteoblast differentiation and bone formation.[72] When cultured with growth factor-rich materials like PRF, DFSCs exhibit improved proliferation, attachment, mineralization, and osteogenic marker expression, enhancing their potential for use in maxillofacial surgery and bone defect repair, ultimately improving clinical outcomes in tissue regeneration.[72]

DISCUSSION

ORN is a common and challenging condition that is difficult to manage due to obstacles in understanding its pathogenesis and establishing a definitive clinical definition or uniform classification. The molecular pathogenesis remains unclear, complicating effective management. Despite challenges, recent clinical advances include better identification of ORN risk factors and the development of animal models that closely resemble human disease, enhancing our understanding of its pathogenesis. Preclinical trials in these models may also provide early insights into prevention and treatment efficacy.

Before conducting surgical care for dental conditions in high-risk environments, nonsurgical options should be considered (such as decoronating crowns with/without root canals and leaving the structure in situ), or employing medical interventions outlined above to support wound healing and reduce the risk of necrosis. Outside of surgical treatment, definitive medical management has been difficult to achieve and in cases where ONJ progresses, medical management approaches may enhance the surgical outcomes. Given the extremely challenging microenvironment and lack of endogenous progenitor cells that can contribute to bone formation, restoration or replenishment of a progenitor compartment in a depleted environment is an attractive clinical concept. Cell-based treatments hold promise in the regeneration of bone in other clinical contexts. Given the early success of iPSC in bone regeneration in the context of other bony defects (eg, spine and cranial bone), these cells may hold promise in restoring the cellular balance that is required for normal bone homeostasis and potentially reversing the course of ORN in the mandible. Further refinement and testing of these cells in animal models will be critical for determining if cell-based therapies are a viable clinical option in the management of ORN.

Although multiple case reports have suggested that ORN can potentially be treated with cell-based therapies, debate continues regarding the optimal source of the cells. iPSCs have shown a great deal of clinical promise and may be the optimal building blocks for the reconstruction of complex defects given the ability of these cells to differentiate into multiple lineages of cells. Optimizing treatment for ORN will have to overcome the myriad challenges of the microenvironment of the disease, including the lack of vascularization, compromised immune system, and proximity to oral cavity flora. Furthermore, in restoring the bone of the mandible, it is necessary to provide robust bone stock that can withstand the strength necessary for mastication. This treatment, therefore, should include a combination of a robust scaffold, highly osteogenic stem cells, osteogenic factors, neovascularization signals and stimulation of wound repair. Now that the appropriate preclinical animal models exist, it will be possible to test various scaffolds and combinations of cell-based treatments that will hopefully provide guidance supporting the best future approaches to the management of this challenging disease.

Current treatment strategies for ORN face several limitations. Some nonsurgical interventions for ORN have limited evidence supporting their long-term efficacy, as they appear to offer benefits primarily in mild to moderate stages, with less predictable outcomes in advanced cases. Emerging therapies also require further validation. While surgical management strategies for ORN are generally guided by disease severity, current recommendations are largely based on clinical staging systems and expert consensus, with limited high-level evidence directly comparing outcomes across different surgical approaches. In addition, a 2014 review suggests the use of fibular vascularized bone grafts for reconstructing defects larger than 6 cm,[73] whereas autogenous nonvascularized bone grafts are typically preferred for smaller defects, under 5 to 6 cm, especially in well-vascularized, noninfected sites.[74–77] Our search criteria might not have fully captured all articles that discuss all nonsurgery and surgical treatments. Further limitations of this study include the use of several studies with retrospective designs, which may introduce potential selection bias.

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