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Emerging Intra-Articular Drug Delivery Systems for the Temporomandibular Joint

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Abstract

Temporomandibular joint (TMJ) disorders are a heterogeneous group of diseases that cause progressive joint degeneration leading to chronic pain and reduced quality of life. Both effective pain reduction and restoration of TMJ function remain unmet challenges. Intra-articular injections of corticosteroids and hyaluronic acid are currently used to treat chronic pain, but these methods require multiple injections that increase the risk of iatrogenic joint damage and other complications. The small and emerging field of TMJ tissue engineering aims to reduce pain and disability through novel strategies that induce joint tissue regeneration. Development of methods for sustained, intra-articular release of growth factors and other pro-regenerative signals will be critical for the success of TMJ tissue engineering strategies. This review discusses methods of intra-articular drug delivery to the TMJ, as well as emerging injectable controlled release systems with potential to improve TMJ drug delivery, to encourage further research in the development of sustained release systems for both long-term pain management and to enhance tissue engineering strategies for TMJ regeneration.

Keywords

Temporomandibular Joint; Temporomandibular Disorder; Intra-articular; Drug delivery; Sustained release; Inflammation; Tissue engineering; Corticosteroid; Hyaluronic acid; Microparticle; Nanoparticle; Liposome; siRNA

Introduction

Temporomandibular joint (TMJ) disorders are the main cause of chronic facial pain and a major cause of disability. Treatment of these disorders in the United States has an estimated cost of \$4 billion per year [1]. Unlike other degenerative joint diseases, which are more common in the elderly, TMJ disorders affect up to one-third of adolescents and young adults. The chronic pain associated with progressive TMJ degeneration limits talking, chewing, and other basic daily activities [2,3]. Current treatments for TMJ disorders are limited. In severe cases, both effective pain reduction and restoration of TMJ function remain an unmet challenge [4].

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One main type of TMJ disorder is an osteoarthritis-like degenerative joint disease characterized by progressive bone and cartilage destruction and subsequent inflammation, which exacerbates joint tissue catabolism [5]. Consequently, pharmacologic approaches to TMJ disorders have paralleled those for symptomatic treatment of osteoarthritis, including non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular injections of either steroids or hyaluronic acid into the superior joint space (see Figure 1). However, use of these agents remains controversial in light of decades of mixed reports of intra-articular injections either accelerating TMJ destruction or triggering regeneration [6]. As in the case of osteoarthritis, no agents are available to reverse the underlying TMJ disease. Consequently, current pain reduction techniques are effective in the early stages of the disease, but fail to alleviate the severe, chronic pain caused by advanced joint degeneration [5,7].

There is a need for sustained release agents that effectively reduce pain and have minimal systemic side effects, enabling long-term administration without the disastrous ectopic effects seen with NSAIDs like rofecoxib (Vioxx®) [8]. This review discusses methods of intra-articular drug delivery to the TMJ, as well as emerging injectable controlled release systems with potential to improve TMJ drug delivery, to encourage further research in the development of sustained release systems for both long-term pain management and to enhance tissue engineering strategies for TMJ regeneration.

Current Methods of Intra-Articular Injection

A variety of injectable corticosteroid and hyaluronic acid formulations are used to reduce the persistent pain associated with TMJ destruction. Localized drug delivery via intra-articular injections minimizes ectopic effects while alleviating joint pain and other symptoms. Although the Food and Drug Administration (FDA) has only approved intra-articular hyaluronic acid formulations for osteoarthritis of the knee, these formulations are still used to treat pain in a number of other joints, including the TMJ [5,9].

Studies of the efficacy of intra-articular TMJ injections have shown mixed results, with improvement in some patients and disease progression in others [6]. Alarming reports of post-injection complications, including cartilage destruction, bone necrosis, and progression of joint disease, have discouraged their use for TMJ pain [10,11]. These reports often describe isolated patients given repeated intra-articular injections [11-13]. High doses of corticosteroids are known to increase the risk of aseptic bone necrosis. In one case report, a previously asymptomatic patient with TMJ inflammation developed disc dislocation, chondrolysis, heterotopic bone formation, and necrosis of the articular tubercle following repeated, high doses of intra-articular corticosteroid (triamcinolone). Surgery was necessary to correct the resulting joint degeneration and limited range of motion [12]. In contrast, hyaluronic acid itself does not cause bone necrosis. This complication has nevertheless been reported following hyaluronic acid injections to the TMJ, and is attributed to bone trauma occurring during the intra-articular injection procedure [11,14]. This section reviews the efficacy of corticosteroid and hyaluronic acid injections for TMJ disorders, and highlights the unmet needs in existing intra-articular drug delivery strategies.

Corticosteroids

Reports of intra-articular corticosteroid injections to the TMJ date back to over 50 years ago [15]. Numerous corticosteroid formulations are available for intra-articular injection, ranging from solutions of more soluble agents to suspensions of triamcinolone hexacetonide and other relatively insoluble steroids. Although the efficacy of various corticosteroids is presumed to differ, studies of this topic have been limited [7,16,17]. A variety of methods are currently used for intra-articular corticosteroid injection to the TMJ, each with the goal of minimizing the potential for tissue damage.

Intra-articular corticosteroid formulations are often diluted with a local anesthetic prior to injection into the TMJ [18-20]. This method is thought to decrease the risk of soft tissue atrophy and other complications, although evidence supporting this claim is largely anecdotal [16, 17]. In a controlled study of adults with TMJ arthritis, a single intra-articular injection of corticosteroid (methylprednisolone) diluted with lidocaine significantly reduced joint pain and other symptoms for 4-6 weeks [20]. The pharmacologic effect of intra-articular methylprednisolone lasts 3-4 weeks, so these findings were consistent with the expected timeline of corticosteroid effect. No adverse events were reported [20].

The most common treatment strategy is either a single injection [19-23] or a series of two injections spaced 14 days apart [24-28], although the best method has yet to be determined. Some clinicians have suggested that a single corticosteroid injection is beneficial for patients with severe TMJ pain, while further injections do not provide added pain relief, and may increase the risk of joint degeneration and other complications [12,21]. In a recent study of patients with TMJ arthritis, there was a significant improvement in TMJ mobility and symptoms, particularly pain and difficulty eating, following the first corticosteroid (triamcinolone) injection. No significant improvement was seen in patients given further injections, suggesting that a single injection is of greatest utility. One patient even developed subcutaneous atrophy after receiving a total of 5 injections to a single TMJ and required surgery [29]. This isolated case underscores the need for new methods of intra-articular drug delivery, particularly sustained release formulations, which would eliminate the need for numerous injections, each of which induces further damage to already degenerating TMJ tissue.

Several decades ago, Toller [21] suggested that intra-articular corticosteroid injections were only useful in adult patients with TMJ disorders; a single intra-articular injection resulted in resolution of TMJ pain and other symptoms in 62% of adult patients, compared to only 17% of pediatric patients [21]. However, the efficacy may vary depending on the specific cause of TMJ degeneration. In recent studies of juvenile idiopathic arthritis, intra-articular corticosteroid (triamcinolone) injections improved or even completely eliminated TMJ pain in 77-88% of children for several months [22,23,29]. Despite the young age of the patients, adverse events (e.g. facial swelling, asymptomatic intra-articular calcifications, and subcutaneous atrophy) were rare in these studies. This likely reflects the cautious injection methods used, which included general anesthesia and costly radiographic needle guidance [22,23,29].

As with any clinical technique, the accuracy of placement of intra-articular injections depends upon the experience of the medical practitioner. An estimated one-third to one-half of all steroid and hyaluronic acid injections are inaccurately placed, although the impact of this extra-articular placement on therapeutic efficacy and clinical outcome remains unclear [30,31]. Extra-articular injection of corticosteroids may be more difficult to detect based on patient symptoms because steroid formulations are less viscous than hyaluronic acid preparations, making it more likely that an extra-articular injection of corticosteroid would be painless [28]. Needle placement can be confirmed with radiographic or arthroscopic techniques, but these techniques are inconsistently used because they are not considered cost-effective in many cases. Imaging guidance during intra-articular TMJ injection can double the cost of the procedure [29]. Novel methods of long-term intra-articular drug delivery would decrease the number of injections needed and thus decrease the financial burden associated with needle-guidance techniques and other precautions.

Radiographic imaging is a common method of monitoring the progression of TMJ disorders. Long-term follow-up studies of patients receiving intra-articular corticosteroid injections indicate sustained improvement in TMJ pain and, in some cases, radiographic regression of joint disease after 8-12 years [32,33]. However, TMJ degeneration continues to worsen in many

cases [25,29]. Patients with severe damage may be less responsive to intra-articular corticosteroids [18], and require multiple injections to treat persistent, severe TMJ symptoms [23,29]. New methods of intra-articular drug delivery will enable tighter control over the release profile of these agents.

Hyaluronic Acid

Intra-articular hyaluronic acid, also called hyaluronan or sodium hyaluronate, has been used for nearly two decades to treat TMJ disorders [14,34,35]. Hyaluronic acid (HA) is a normal product of joint tissues that is continuously released into the synovial fluid, where it serves as a lubricant, anti-inflammatory, and pain-reliever. Findings of reduced HA molecular weight and concentration in arthritic joints inspired the development of injectable preparations to restore the properties of synovial fluid, so-called viscosupplementation [36]. In TMJ disorders, intra-articular HA is used in two different treatment strategies. It is administered alone for viscosupplementation, and is also used as an adjunct to arthrocentesis, a surgical procedure where the joint is flushed to remove inflammatory mediators [37]. The goal of both methods is to relieve TMJ symptoms and reduce inflammation.

The most common viscosupplementation strategy is a series of either 2 intra-articular HA injections spaced 7-14 days apart [24-28,38-40], or 5 injections each 7 days apart [11,41-43]. In comparison to corticosteroids, a greater number of HA injections are typically administered because HA has fewer potential complications [27]. However, a randomized, double-blind, placebo-controlled trial concluded that even a single HA injection has a beneficial effect; patients with TMJ disc displacement had sustained, significant improvement in symptoms and joint mobility for 6 months [14]. Intra-articular HA injections not only reduce pain and improve TMJ function, but also reduce the concentration of various inflammatory mediators in the synovial fluid [38]. Since the half-life of HA within the joint is very short, some have proposed that this anti-inflammatory function is a more likely mechanism for the long-term effects of viscosupplementation, while others have suggested that short-term improved lubrication may interrupt the cycle of tissue damage and inflammation [39,40].

A variation on the viscosupplementation method, so-called pumping injection of HA, has shown great promise as a non-surgical therapy for patients with severely limited mouth opening (TMJ closed lock) [34,41-44]. In this technique, a local anesthetic is first injected into the synovial fluid, and the TMJ is then “pumped” by drawing the fluid into and out of the syringe. After pumping several times, most of the synovial fluid is aspirated and replaced with an intra-articular injection of HA [43]. The pumping method provides significant improvement in TMJ pain and joint mobility for months to years [41-44]. In a study of patients with non-reducing TMJ disc displacement, 82% of patients continued to be free of pain 2 years after treatment, even though the disc displacement remained uncorrected [43]. However, pumping injections significantly increase the risk of further bone degeneration [44], which may be the result of repeated micro-trauma from the syringe tip [11]. Novel slow release HA formulations would decrease the number of injections necessary, reducing iatrogenic joint damage.

The multi-functionality of hyaluronic acid, including lubrication, anti-inflammatory, and analgesic properties, led to the use of intra-articular HA as an adjunct to TMJ arthrocentesis. In this minimally invasive surgical technique, two needles are inserted and the joint space is flushed with about 50-300 mL of saline or Ringer's lactate, an electrolyte solution. In the combined strategy, HA is injected into the TMJ after arthrocentesis is completed [45,46]. As in viscosupplementation, a common regimen is a series of 5 treatments at weekly intervals [46-48]. Although an early trial comparing the combined strategy with traditional TMJ arthrocentesis showed no difference on patient outcome [35], a recent randomized trial indicated the combination therapy was more effective in reducing TMJ pain and improving

function for 2 years [45]. In another study, 70% of patients reported complete resolution of pain 6 months after combined treatment [46].

A recent systematic review and meta-analysis of all randomized, controlled trials of intra-articular HA injections for TMJ disorders concluded that existing evidence is insufficient to either support or refute the benefit of HA injections [49]. Meta-analysis of viscosupplementation studies found no statistically significant short-term improvement compared to placebo (saline) injections, although there was some evidence of long-term benefit. Analysis of HA as an adjunct to arthrocentesis was inconclusive due to a lack of randomized, controlled trials on this topic [49]. Although further validation is needed, preliminary studies of HA are promising, as emphasized by studies directly comparing this treatment to intra-articular corticosteroids.

Comparison

Several randomized comparisons of intra-articular hyaluronic acid (sodium hyaluronate) and corticosteroid (betamethasone) TMJ injections have shown no significant difference between the two treatments [25-27]. A meta-analysis of studies from 1985-2002 found no statistically significant short- or long-term benefit of intra-articular HA over corticosteroid injections on improving TMJ disorder symptoms [49]. However, in a recent randomized, blinded study, hyaluronic acid injections reduced pain to a greater extent than corticosteroids [28]. Both treatments resulted in sustained, significantly reduced TMJ symptoms and improved joint mobility for 1-2 years [27]. Such significant positive effects on TMJ range of motion were not seen with placebo (saline) injections [24]. Radiographic imaging indicated that equal proportions of each treatment group had stable, improved, and worsened joint degeneration [25], and an equal number of transient side effects were reported for both treatments [28]. Mixed reports of the efficacy of intra-articular injections may be a reflection of the heterogeneous nature and etiology of TMJ disorders. Further controlled studies are needed to determine the precise impact of intra-articular injections.

Limitations of Current Intra-Articular Injections

Current methods of intra-articular drug delivery often require frequent injections that have a high financial burden, impact patient quality of life, and also increase the risk of complications. Immediately following each intra-articular injection, patient joint activity (e.g. chewing, talking, etc.) is restricted so as to minimize the risk of either joint overload or tissue reaction resulting in increased drug clearance [5,7,39]. Although reports of adverse events, particularly following HA injection, are rare, it is unclear whether this reflects reality. Many older studies focused on positive treatment effects, with inconsistent reporting of adverse events [28,48]. Slow-release intra-articular medications have the potential to eliminate many of these concerns. An increased duration of drug release would decrease the number of injections necessary, reducing both the risk of iatrogenic injury and limitations on patient activity.

Animal Models for Investigating the Efficacy of Intra-Articular Injections

Animal models are a useful tool for understanding the pathophysiological mechanisms underlying TMJ disorders, and for evaluating the efficacy of intra-articular injections. A variety of animal models have been used to evaluate various aspects of drug delivery to the TMJ, including adverse effects of existing intra-articular formulations and the efficacy of emerging treatments.

Small animal models, such as rats and rabbits, have been used to study the adverse effects of currently used intra-articular corticosteroid and hyaluronic acid formulations, given the concerns that complications are under-reported. Rabbit models have been used to study the

effect of both corticosteroid and HA injections on TMJ inflammation [50,51]. A recent study comparing arthrocentesis, viscosupplementation, and combination therapy found that arthrocentesis did not prevent TMJ degeneration in rabbits, but did have a synergistic effect when used in combination with HA injections [51]. Recent studies using rodent models found that both corticosteroid and hyaluronic acid injections caused soft tissue inflammation [52, 53]. Several corticosteroid preparations induced soft tissue atrophy and necrosis in a rat model [53]. Although intra-articular corticosteroid (dexamethasone) injections significantly reduced TMJ inflammation in another rat model, increased osteoclast activity was noted on histological analysis of the mandibular condyle, raising concerns that intra-articular injections may increase the rate of bone resorption [54]. However, the implications for the treatment of human patients are unclear because susceptibility to post-injection joint degeneration varies among species, and may even vary by individual. Repeated intra-articular corticosteroid injections in a primate model at exceedingly high dosages had few adverse effects, in contrast to the severe post-injection joint degeneration seen in a rabbit model [55].

Rodent models are commonly used in studies of TMJ damage and transmission of pain signals to the brain (nociception). Rat models of TMJ inflammation have been developed using a variety of methods ranging from repeated, manual, forced mouth opening to intra-articular injection of complete Freund's adjuvant, a pro-inflammatory agent [54,56]. Inspired by painful, impaired eating in human patients, computerized meal pattern analysis has been developed as a non-invasive method of quantifying TMJ pain in rat models [56-59]. Rats are housed in individual cages equipped with photobeam computer-activated pellet feeders. When a rat consumes a food pellet from the device, an infrared beam at the base of the feeding tray is no longer blocked. The beam is detected, and a signal is sent to a computer, which records the date and time and dispenses a new food pellet; over time, this generates a record of the animal's feeding behavior [57]. Longer meal duration has been verified as a specific marker of TMJ inflammation and pain [58,59]. Meal pattern analysis has been used to study the efficacy of several oral and injectable pharmacologic agents [56-59], and is a promising non-invasive tool for evaluating emerging intra-articular drug delivery systems.

Larger animals such as sheep, pigs, or primates may be preferable if intra-articular injection of drug delivery systems is not feasible in a small animal model. Given the prohibitively high cost of primate studies, pigs are currently considered the ideal choice for biomechanical and tissue engineering studies, since their TMJ anatomy is quite similar to that of humans [4,60, 61]. A recent study in a porcine model of TMJ degeneration indicated that HA viscosupplementation decreases friction on joint cartilage by 50% [62]. In an ovine (sheep) model, a series of 5 intra-articular HA injections slowed disease progression more than placebo (saline) and significantly reduced the extent of TMJ damage for 3 months [63,64]. Together with less costly rodent and rabbit models, these large animal models will be useful tools for validating the efficacy of emerging intra-articular drug delivery systems.

Emerging Intra-Articular Drug Delivery Systems

Current methods of intra-articular drug delivery are complicated by rapid degradation and clearance of injected pharmacologic agents, so that frequent injections and high concentrations are necessary. Microcarrier-based drug delivery systems, including hydrogels, polymeric microparticles, and liposomes, are well-established as methods for sustained release in extra-articular applications. Over the past two decades, several reports have described the use of controlled release systems for intra-articular applications, but most of these strategies have been evaluated in animal models of knee osteoarthritis and other knee joint disorders [see recent reviews [7,65]]. This section discusses microparticles, liposomes, and other emerging drug delivery systems that promise to greatly improve intra-articular drug delivery to the TMJ.

Intra-articular hyaluronic acid formulations consist of colloidal dispersions of HA in aqueous solution, which form hydrogel structures [7]. In the United States, these agents are the only microcarrier-based intra-articular formulations available for clinical use in any joint. However, as previously stated, intra-articular HA injections are not yet FDA-approved for use in the TMJ [5,9]. Nevertheless, recent progress in the field of injectable biomaterials shows great promise for the development of superior intra-articular therapies. Novel HA-based materials have the potential to improve viscosupplementation and joint regeneration strategies [66,67]. In a recent study, intra-articular delivery of basic fibroblast growth factor using an HA vehicle significantly improved osteochondral repair in the knee joint of a rabbit model [68]. Injectable, biodegradable hydrogels have shown promise for delivery of cells and growth factors promoting cartilage regeneration [69-71]. Adaptations of these drug delivery systems have the potential to enhance TMJ drug delivery and tissue engineering strategies.

Polymeric nano- and microparticles made from a variety of natural and synthetic materials, including albumin, gelatin, and poly(lactic-co-glycolic acid) (PLGA) are being investigated for intra-articular sustained release applications [see recent reviews [7,65]], as summarized in Table 1. In one study, rat knee joints injected with microencapsulated versus aqueous (free drug solution) formulations had a 10-fold difference in NSAID concentration after 24 hours [72]. Reports of joint inflammation *in vivo* following intra-articular injections of gelatin and chitosan microparticles have caused some concern. Although the cause remains unclear, it has been suggested that these reactions may reflect impurities in the commercially available biomaterials used to create these microparticles, and not an intrinsic proinflammatory property of gelatin and chitosan [73,74]. For instance, a recent study in a rabbit model indicated that intra-articular delivery of basic fibroblast growth factor via gelatin microparticles improved knee joint swelling, proteoglycan expression, and histological appearance of arthritic tissue [75]. At the same time, a variety of synthetic carriers, including poly(caprolactone) (PCL)-, poly(L-lactic acid) (PLLA)-, PLGA-, poly(propylene sulphide) (PPS)-, and polyphosphazene-based nano- and microparticles, have also shown promise for intra-articular applications [74, 76-79] (see Table 1). The ideal material remains to be elucidated. The optimal size range for intra-articular drug delivery systems is also debated, with some studies reporting that nanoparticles are superior [80,81], while others support the use of microparticles [74,82]. These and other design parameters will need to be optimized in the development of intra-articular methods of sustained release for the TMJ.

A liposomal corticosteroid formulation containing dexamethasone-21-palmitate (Lipotalon®) available in Germany is the only intra-articular liposomal product used in human patients [7]. As with microcarriers, many preclinical studies have investigated the efficacy of intra-articular liposomal drug delivery systems [see recent review [65]]. In an effort to eliminate joint injections altogether, intravenous administration of these preparations has also been evaluated. However, in a recent study, intravenous administration of a liposomal formulations of an anti-inflammatory agent failed to treat arthritic symptoms in a rat model [83]. In contrast, a single intra-articular injection suppressed rat knee joint inflammation for 3 weeks. Large multilamellar (micro-scale) liposomes were more effective than small unilamellar (nano-scale) liposomes [84]. These novel controlled release systems may provide a better solution for intra-articular administration of various compounds to the TMJ.

One particularly promising application is intra-articular delivery of small interfering ribonucleic acids (siRNAs), endogenous molecules that “silence” specific genes by binding to messenger RNA and blocking protein translation [85,86]. Although synthetic siRNA formulations that suppress the vascular endothelial growth factor pathway are already in clinical trials for treatment of pathologic neovascularization within the eye [85,86], development of joint therapeutics remains in the preclinical stage. A major challenge is the lack of a method for intra-articular sustained release [87,88]. In two recent studies in rodent

models of knee arthritis, intra-articular delivery of siRNA targeting tumor necrosis factor- α (TNF- α), a proinflammatory cytokine, significantly reduced inflammation and exerted a chondroprotective effect for several weeks [89,90]. A similar beneficial effect on murine knee joint inflammation was reported with systemic administration of anti-TNF- α siRNA complexed with cationic liposomes [91]. However, all of these strategies required multiple injections to achieve these positive effects. Long-term treatment of joint disease via siRNA will require novel sustained release strategies. Various groups are already investigating methods of intra-articular siRNA delivery in animal models of TMJ inflammation, and preliminary findings are promising.

Emerging methods of intra-articular drug delivery have the potential to overcome many of the limitations of existing intra-articular formulations. To our knowledge, none of the strategies discussed in this section has yet been evaluated in a TMJ model. Novel systems for sustained release will increase the residence time of medications within the joint, reducing the need for repeated intra-articular injections and thus minimizing iatrogenic damage. Tighter control over release kinetics would reduce the required medication dosage and decrease the risk of ectopic effects.

Importance of Drug Delivery for TMJ Tissue Engineering

Advances in the field of drug delivery will improve pain management and also aid progress in the emerging field of TMJ regeneration. The standard treatment for severe TMJ degeneration is currently surgical joint replacement [92]. Research in TMJ repair and regeneration has proceeded at a cautious pace following the experience with early alloplastic TMJ implants, whose tendency for premature failure triggered immune reactions resulting in catastrophic joint damage [4,93]. Although improved products are currently available for total joint replacement, even these have a limited lifetime. The potential need for serial surgeries to replace worn out prostheses has raised concerns, since numerous clinical studies have indicated that serial TMJ surgeries often result in joint mutilation [92,94].

Drug delivery systems can be used to either modify the joint environment prior to implantation, or to deliver proregenerative signals in a spatially and temporally controlled fashion, so as to trigger joint healing while avoiding systemic drug release, ectopic effects, and other such complications. The limitations of current therapeutic strategies for TMJ disorders have led to increased interest in tissue engineering strategies, which combine cells, bioactive factors, and implantable scaffolds to trigger joint regeneration [95]. However, TMJ tissue engineering remains a small and emerging field. Research to date has focused on separately engineering the fibrocartilagenous TMJ disc and mandibular condyle, with few preclinical or *in vivo* studies [see recent reviews of TMJ disc [96,97] and mandibular condyle tissue engineering [98]].

Since joint tissue, particularly the fibrocartilagenous disc, has very limited healing capacity, TMJ tissue engineering strategies must deliver key growth factors and other molecular signals that induce joint regeneration [99]. Development of systems for controlled release of these factors will be critical to the success of TMJ regeneration [100]. Tissue engineered products may never work properly unless researchers identify and find a means to control the underlying joint degeneration. The emerging intra-articular drug delivery systems described in this paper have the potential to both treat pain associated with TMJ disorders and deliver growth factors and other signals to control the underlying joint degeneration.

Concluding Remarks

TMJ disorders are a group of degenerative joint diseases that cause progressive damage to the fibrocartilagenous TMJ disc, mandibular condyle, and synovial tissues. Although there has been significant progress in both drug delivery and joint tissue engineering, challenges still

remain, including the need for sustained release preparations and minimally invasive tissue engineering approaches to reduce iatrogenic joint damage. Tissue engineering efforts have separately focused on the mandibular condyle and TMJ disc. However, it seems unlikely that the disc could be implanted alone, so future efforts will need to focus on developing an implantable disc-condyle combination. In addition to providing a means of sustained release of pain-relieving medications, intra-articular controlled release systems have the potential to play a crucial role in the clinical implementation of tissue engineering strategies for TMJ regeneration.

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Abbreviations

b-FGF	basic fibroblast growth factor
FDA	Food and Drug Administration
HA	hyaluronic acid
NSAIDs	non-steroidal anti-inflammatory drugs
PCL	poly(caprolactone)
PLGA	poly(lactic-co-glycolic acid)
PLLA	poly(L-lactic acid)
PPS	poly(propylene sulphide)
RNA	ribonucleic acid
siRNA	small interfering ribonucleic acid
TMJ	temporomandibular joint
TNF	tumor necrosis factor

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Figure 1a

Figure 1b

Figure 1.

Schematic depicting the temporomandibular joint (TMJ), indicated by the red box in (a). The second image (b) shows relevant components of joint anatomy, including the TMJ disc, the head of the mandibular condyle, and a portion of the connective tissue capsule that envelops the joint. The superior joint space is also specifically indicated, and it is into this space that intra-articular TMJ injections are made.

Table 1Particulate Intra-articular Drug Delivery Systems That Have Been Studied *In Vivo*

Delivery System	Drugs	Animal Models	References
Albumin microparticles	Diclofenac sodium (NSAID)	Rabbit knee	[82]
Chitosan microparticles	Celecoxib (NSAID), Paclitaxel	Rat knee, Rabbit knee	[72,74]
Gelatin microparticles	b-FGF	Rabbit knee	[68,75]
Gelatin/chondroitin-6-sulfate microparticles	Albumin, Catalase	Mouse knee	[73]
PCL microparticles	Paclitaxel	Rabbit knee	[74]
PLGA microparticles	Paclitaxel, Diclofenac sodium (NSAID)	Rabbit knee, Rat knee	[74,76,80]
PLGA nanoparticles	Betamethasone	Rat knee, Rabbit knee	[80,81]
PLLA microparticles	Paclitaxel	Rabbit knee	[74]
Polyphosphazene-based nanoparticles	Indomethacin (NSAID)	Rat ankle	[78,79]
PPS nanoparticles	Oligopeptide	Mouse knee	[77]