The Potential Role of Doxycycline in the Treatment of Osteoarthritis of the Temporomandibular Joint
H.A. Israel, N.S. Ramamiurthy, R. Greenwald and L. Golub
ADR 1998 12: 51
DOI: 10.1177/08959374980120012001
The online version of this article can be found at:
http://adr.sagepub.com/content/12/1/51

Published by:
SAGE
http://www.sagepublications.com
On behalf of:
International and American Associations for Dental Research

Additional services and information for Advances in Dental Research can be found at:

Email Alerts: http://adr.sagepub.com/cgi/alerts
Subscriptions: http://adr.sagepub.com/subscriptions
Reprints: http://www.sagepub.com/journalsReprints.nav
Permissions: http://www.sagepub.com/journalsPermissions.nav

>> Version of Record - Nov 1, 1998
What is This?
THE POTENTIAL ROLE OF DOXYCYCLINE IN THE TREATMENT OF OSTEOARTHRITIS OF THE TEMPOROMANDIBULAR JOINT

H.A. ISRAEL1*
N.S. RAMAMURTHY2
R. GREENWALD3
L. GOLUB2

1Columbia University, New York, New York; 2State University of New York at Stony Brook; and 3Long Island Jewish Medical Center, New Hyde Park, New York; *corresponding author

Abstract—Collagenase and gelatinase are matrix metalloproteinases (MMPs) which play an important role in tissue destruction in arthritic joints. Studies have demonstrated that tetracyclines can inhibit MMPs and prevent tissue destruction independent of their antimicrobial activity. The purpose of this pilot study is to assess the potential therapeutic role of Doxycycline in patients with advanced osteoarthritis of the temporomandibular joint (TMJ).

This ongoing investigation includes patients with a diagnosis of osteoarthritis of the TMJ based on clinical and diagnostic imaging findings, symptoms (localized TMJ pain, limited mobility, dysfunction) for a minimum of 36 months, and failure of previous non-surgical and surgical modalities to alleviate the symptoms. A synovial fluid sample is collected by a saline injection and aspiration technique, followed by diagnostic arthroscopy. Patients are placed on Doxycycline 50 mg BID for three months and then undergo repeat diagnostic arthroscopy and synovial fluid collection. The samples are stored at -80°C. Collagenase activity is determined by a combination of SDS-polyacrylamide gel electrophoresis and fluorography and calculated based on the percentage of collagen alpha chains that are degraded into alpha breakdown products.

Three patients have completed the three-month course of Doxycycline thus far, and 5 joints with osteoarthritis have been analyzed. All patients were female (mean age = 35, mean duration of symptoms = 132 months) and had undergone previous bilateral arthroscopies. One patient had undergone unilateral arthroplasty. The mean collagenase activity showed 55% collagen lysis prior to Doxycycline treatment and 19% after three months of therapy. The mean gelatinase activity was 28% prior to Doxycycline treatment and 7% after three months of therapy. The mean interincisal opening was 33 mm initially and 41 mm after three months of Doxycycline. Subjectively, two of the three patients reported significant improvement in their overall symptoms, which they had not experienced over the previous three years. One patient did not experience any change in symptoms, in spite of a marked reduction in collagenase activity from 86.4% to 9.6%.

Because of the very small numbers of patients enrolled in this pilot study so far, no statistically significant differences could be appreciated. However, the dramatic reduction in collagenase activity in these patients, with a long history of TMJ symptoms from osteoarthritis, suggests the potential promising role of Doxycycline in the management of osteoarthritis, and further investigation is warranted.

Key words: Temporomandibular joint, osteoarthritis, doxycycline.

OSTEOARTHRITIS OF THE TEMPOROMANDIBULAR JOINT

Recent research on the biochemical events associated with temporomandibular disorders has demonstrated the importance of osteoarthritis as a major pathology in the temporomandibular joint. Osteoarthritis has been defined as a functional disorder characterized by altered joint anatomy associated with degeneration and loss of articular cartilage (Stegenga et al., 1989, 1991; Bullough, 1992). While osteoarthritis has been associated with a level of chronic inflammation (Revell et al., 1988; Myers et al., 1992), the role of this inflammatory component in the degradative process has not been clearly identified. Furthermore, the enzymes responsible for the destruction of connective tissue within the temporomandibular joint have not been clearly identified.

The importance of degeneration of articular cartilage in the pathogenesis of temporomandibular joint disease has been emphasized in numerous studies (Stegenga et al., 1989, 1991; Israel et al., 1991; Dijkstra et al., 1995; Milam and Schmitz, 1995; Ratcliffe and Israel, 1995). It has been proposed that articular cartilage degeneration may lead to compensatory or pathologic changes in the surrounding tissue (synovium, ligaments, muscle, and subchondral bone), resulting in common symptoms of craniomandibular dysfunction such as impaired joint movement, clicking, locking, crepitus, and pain.

Articular cartilage of the TMJ is an important functional...
tissue that permits load-bearing and functional movements of the joint. It consists of an extensive extracellular matrix containing primarily collagen, proteoglycans, and water, and is synthesized and maintained by a sparse population of cells, the chondrocytes. The upper zone of the cartilage of the TMJ is fibrous, which covers a lower, more cartilaginous layer. The disc also contains fibrous and cartilaginous regions. The degeneration of the articular tissues involves morphologic changes that can be seen arthroscopically, such as roughening of the smooth surface, fibrillation, fissuring, and ultimately loss of tissue (Bullough, 1992). Compositional and metabolic changes include an increase in water content, disruption of the collagen network, and accelerated breakdown and loss of the proteoglycans (Israel et al., 1991; Dijkgraaf et al., 1995; Ratcliffe and Israel, 1995). The chondrocytes are able to modify their metabolic activities in response to the changing environment, but ultimately an imbalance of synthesis and catabolism will lead to matrix degeneration (Mow et al., 1992; Dijkgraaf et al., 1995; Ratcliffe and Israel, 1995). Matrix components are degraded and are released from the articular cartilage into the synovial fluid. When accelerated loss occurs, the matrix components may be detected in the synovial fluid at elevated levels (Saxne et al., 1986; Ratcliffe et al., 1988; Lohmander et al., 1993, 1994). Therefore, it is possible to detect and monitor disease activity by studying the level of matrix components in the synovial fluid (Lohmander, 1994; Ratcliffe et al., 1995).

Arthroscopic surgery and arthrocentesis are recent treatments for patients with painful limitation of temporomandibular joint function; these treatments have enabled studies of human TMJ synovial fluid to be conducted. Arthroscopic diagnosis of joint morphology, together with analysis of the synovial fluid from the same joint, has allowed detailed studies of human TMJ pathology to be undertaken. In the synovial fluid of patients with arthroscopically diagnosed synovitis, elevated levels of prostaglandin E\textsubscript{2} and leukotriene B\textsubscript{4} have been detected (Quinn and Bazan, 1990). Elevated levels of tumor necrosis factor alpha (TNF\textalpha) in synovial fluid were associated with pre-operative pain in patients with internal derangements who subsequently underwent arthroscopy or arthrotomy (Shafer et al., 1994).

In our laboratory, investigations of TMJ synovial fluid have provided support for the importance of cartilage degradation as a major pathologic entity in the temporomandibular joint (Israel et al., 1991; Ratcliffe and Israel, 1995). We have studied patient populations with significant temporomandibular joint symptoms that failed to resolve with nonsurgical treatment, requiring temporomandibular joint arthroscopy. An arthroscopic diagnosis of osteoarthritis was found to be present in 63% of 95 joints, indicating that osteoarthritis of the temporomandibular joint is a very common entity in patients with severe temporomandibular joint symptoms (Israel et al., 1991; Ratcliffe and Israel, 1995). Elevated levels of keratan sulfate, a sulfated glycosaminoglycan present in cartilage proteoglycans, were found in the synovial fluid of joints that arthroscopically demonstrated osteoarthritis, indicating that proteoglycan degradation is an important event in the pathogenesis of temporomandibular joint disease.

It is clear that a common pathway to temporomandibular joint disease and dysfunction is articular cartilage degradation. Determining markers of articular cartilage degradation in the human TMJ synovial fluid has been important in improving our understanding of the pathogenesis of TMJ osteoarthritis, and, in the future, it may provide us with a marker for monitoring the course of the degradative process. Synovitis is also a common arthroscopic diagnosis in patients with pain in the temporomandibular joint, and often multiple arthroscopic diagnoses are present concomitantly. A recent study has demonstrated both osteoarthritis and synovitis present in 57% of symptomatic temporomandibular joints, suggesting that inflammation plays an important role in the degradative process within the temporomandibular joint (Israel et al., 1997). A furthering of our knowledge of the enzymatic processes responsible for this degradative process has the potential to provide treatment interventions to reduce or stabilize the catabolic events associated with osteoarthritis of the temporomandibular joint.

THE ROLE OF CHEMICALLY MODIFIED TETRACYCLINES IN THE INHIBITION OF CONNECTIVE TISSUE BREAKDOWN

Collagenase and gelatinase are matrix metalloproteinases (MMPs) which play an important role in connective tissue destruction (Golub et al., 1991). In particular, matrix metalloproteinases have been shown to have a key role in connective tissue destruction associated with periodontal disease, non-infected corneal ulcers, and tumor growth and metastasis. Greenwald et al. (1992) have demonstrated that...
matrix metalloproteinases have a significant role in the tissue destruction of arthritic joints. Studies have demonstrated that tetracyclines can inhibit MMPs and prevent tissue destruction independent of their antimicrobial activity (Golub et al., 1991; Greenwald et al., 1992). Analogs of tetracycline used in combination with NSAIDs have been shown to inhibit temporomandibular joint (TMJ) tissue destruction in rats with experimentally induced arthritis (Golub et al., 1991; Greenwald et al., 1992). Ramamurthy et al. (1994) have demonstrated that the combination of a chemically modified tetracycline and a non-steroidal anti-inflammatory inhibited temporomandibular joint destruction in rats with adjuvant arthritis. The purpose of this pilot study is to assess the potential therapeutic role of doxycycline in patients with advanced osteoarthritis of the TMJ.

**MATERIALS and METHODS**

This ongoing investigation has included patients with a diagnosis of osteoarthritis of the TMJ based on clinical and diagnostic imaging findings. Screening procedures include a complete history, clinical examination, and radiographic examination (TMJ panoramic radiographs), and following this, a clinical diagnosis is ascertained. Inclusion criteria for entry into the study are symptoms (localized TMJ pain, limited mobility, dysfunction) for a minimum of 36 months, failure of previous non-surgical and surgical modalities to alleviate the symptoms, and a diagnosis of osteoarthritis of the temporomandibular joint. The clinical diagnosis of osteoarthritis (OA) is based on the presence of crepitus on auscultation of the joint and diagnostic images which reveal erosion, sclerosis, cyst formation, or osteophytic lipping (Mankin and Brandt, 1984; Stegenga et al., 1989). The diagnosis of osteoarthritis is confirmed through diagnostic arthroscopy based on the presence of fibrillated articular cartilage and/or disc perforation (see Fig. 1).

A synovial fluid sample is collected by means of a saline injection and aspiration technique, followed by diagnostic arthroscopy (Murakami and Ito, 1986; Israel, 1992). Patients are placed on doxycycline 50 mg BID for three months and then undergo repeat diagnostic arthroscopy and synovial fluid collection. The samples are stored at -80°C. Collagenase activity is determined from a combination of SDS-polyacrylamide gel electrophoresis and fluorography and calculated based on the percentage of collagen alpha chains that degraded into alphaA breakdown products; gelatinase activity is determined by gelatin zymography (Greenwald et al., 1992). Clinical assessment of patients include a subjective assessment of pain by means of a VAS (visual analog scale, 0 = no pain, 10 = the most severe pain) as well by objective assessment of interincisal opening distance.

**RESULTS**

Three patients have completed the three-month course of doxycycline thus far, and 5 joints with osteoarthritis have been analyzed. All patients were female (mean age = 35, mean duration of symptoms = 132 months) and had undergone previous bilateral arthroscopies. One patient had undergone previous unilateral arthroplasty. The mean collagenase activity showed 55% collagen lysis prior to doxycycline treatment and 19% after three months of therapy (see Figs. 2A, 2B). The mean gelatinase activity was 28% prior to doxycycline treatment and 7% after three months of therapy (see Figs. 3A, 3B).

The mean interincisal opening was 33 mm initially and 41 mm after three months of doxycycline. Subjectively, there was no change in assessment of
Fig. 3A—Mean changes in gelatinase activity in osteoarthritic TMJ synovial fluids demonstrated a marked reduction following 3 months of Doxycycline therapy.  

Fig. 3B—Gelatinase zymography demonstrated reduced gelatinase activity in osteoarthritic TMJ synovial fluids after 3 months of Doxycycline therapy.

pain, with a mean pre-operative VAS of 8 and a mean post-operative VAS of 7.5. One patient did not experience any change in symptoms, in spite of a marked reduction in collagenase activity from 86.4% to 9.6%. There were no significant changes in arthroscopic morphology before and after three months of treatment with doxycycline. However, this was to be expected, since these patients did have a significantly long history of symptoms related to temporomandibular joint arthritis.

The early results from this pilot investigation suggest that the matrix metalloproteinases play an important role in tissue destruction associated with osteoarthritis of the temporomandibular joint. The results also suggest a potentially promising role of doxycycline in the management of osteoarthritis of the temporomandibular joint, and further investigation is warranted.

REFERENCES


CONCLUSIONS

Because of the very small numbers of patients enrolled in this pilot study thus far, no statistically significant differences could be appreciated. However, there was a dramatic reduction in collagenase activity in these patients with a long history of TMJ symptoms from osteoarthritis. Additionally, joint range of motion increased, demonstrating some objective clinical improvement. There was no change in pain or arthroscopic morphology following three months of treatment with doxycycline.


