The Prevalence of Gingival Overgrowth in Rheumatoid Arthritis Patients Treated With Cyclosporin

by

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A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in

THE FACULTY OF GRADUATE STUDIES

DEPARTMENT OF ORAL BIOLOGICAL AND MEDICAL SCIENCES

We accept this thesis as conforming to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA

September 2003

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ABSTRACT

Cyclosporin has been recognized since the mid 1980's as a potent disease-modifying agent for inflammatory auto-immune diseases that are unresponsive to standard therapeutic regimens. From the organ transplant literature, cyclosporin is known to induce gingival overgrowth in the first ninety days of treatment. In Rheumatoid Arthritis (RA), gingival overgrowth, coupled with the common feature of compromised manual dexterity, may make dental plaque control difficult for immunosupressed patients, resulting in increased susceptibility to oral complications. Determination of oral health status has not been included previously in patient evaluations. The goal of this study was to determine the prevalence of gingival overgrowth, predisposing factors and types of oral complications occurring in this population group. The objectives of the study were to determine the prevalence and severity of gingival overgrowth and to determine at what point in the treatment regime the patients were most at risk. Twenty-eight volunteer RA patients took participated in the study. Twenty-two were placed on a cyclosporin treatment regime while six were used as a control group and placed on Methotrexate. Methotrexate is an immunosupressive medication frequently used in the treatment of advanced RA. It does not induce gingival overgrowth but it does produce a high incidence of oral ulceration. At Day Zero, patients were examined by a calibrated examiner to determine probing depths, periodontal attachment loss, maximum opening and gingival inflammation using standard indices. Plaque scores and the presence and severity of gingival overgrowth were recorded. Patients completed a Quality of Life (QOL) Visual Analogue Scale at Day One. Patients were re-examined every four to six weeks for a minimum of six months. At each appointment they were interviewed about

their oral health experiences. Upon leaving the study, participants again completed the QOL visual analogue scale. There was no significant correlation between plaque accumulation and oral complications. Gingival overgrowth was not detected in any of the patients. There was no significant correlation between plaque accumulation and gingival inflammation. Maximum opening scores did not correlate with plaque accumulation scores but did correlate with QOL scores. There was a decrease in gingival inflammation scores through the course of the study.

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ACKNOWLEDGEMENTS

I would like to express my sincere appreciation to all those people who enabled me to complete this project. A special gratitude is extended to the following people.

To all of the kind and patient individuals at the Mary Pack Arthritis Centre, who were willing to give of their time and share their experiences as participants in the study. You made the study possible.

To Mrs. Bonnie J. Craig, Associate Professor and Director, Bachelor of Dental Science Program in Dental Hygiene, Faculty of Dentistry, The University of British Columbia. Your ongoing input throughout this project and a career of twenty years has had a profound effect on my development as a person and a dental hygienist.

To Dr. Hannu Larjava, Professor and Chair, Division of Periodontics and Dental Hygiene, Faculty of Dentistry, The University of British Columbia. I thank Dr. Larjava for inspiration in the area of research while sharing his expertise in research excellence through course work and in the preparation for this study. Thank you for making me think.

To Dr. Jeff Coil, Assistant Professor and Chair, Division of Endodontics, Faculty of Dentistry, The University of British Columbia. Your kind support was most appreciated, as was your input into the final document.

To Dr. Doug Waterfield, Associate Professor and Graduate Advisor, Faculty of Dentistry, The University of British Columbia. I thank Dr. Waterfield for his positive outlook and motivation through a lengthy project. Your input was invaluable as was your support.

To Mrs. Vicki Koulouris, Coordinator of Graduate Studies, Faculty of Dentistry, The University of British Columbia. Thank you for all your time in liasing with graduate studies.

To Mrs. Ingrid Ellis, Research and Administrative Secretary, Faculty of Dentistry, The University of British Columbia. Thank you for your professional input and expertise in the preparation of presentations, proposals and posters.

To my family and friends who showed me their love through support and encouragement. Thank you for making it happen.

To my Mum, who by example, has instilled in me the value of lifelong learning and whose unwavering belief in my capabilities has always motivated me to move on to the next step.

Dedicated to Isabel Emily M^{c}Cloy,

a researcher of life and my Mother.

Chapter 1: Rheumatoid Arthritis

The word "Rheumatism" is derived from the ancient Greek word "rheumatismos" which denoted mucus as "evil secretions" that flowed from the brain to the joints producing pain. Rheumatoid Arthritis (RA) is a systemic auto-immune disorder characterized by persistent joint inflammation. Arthritis and diseases of the joints are among the most common causes of chronic illness in the United States (Wilkins, 1999). Approximately 1% of the population suffers from Rheumatoid Arthritis (RA) and there is no known cure (Machold et al., 1998). If "probable" cases of RA are included (see Table 1), RA sufferers make up 3% or more of the non-institutionalized population of North America. In the United States alone, two million people suffer with RA (ARA, 2003; CDC, 2002). Each year 41 million work-days are lost to the Canadian economy due to lost wages and medical expenses, lost production, and social assistance reaches five billion dollars. RA is responsible for nine million office visits annually in the United States (ACR, 2002). Treatment of RA also has a significant morbidity. In 1992, 1300 Canadians died from gastric ulcers and associated bleeding related to the extensive use of non-steroidal anti-inflammatory drugs (NSAID), routinely recommended for RA pain, compared to 982 Canadians who died from AIDS. Once thought to be a disease of the aged, RA and Juvenile RA strike children and adults throughout their lifespan. Under the age of 60 years, women are more likely to be diagnosed with RA but after 60 years of age the ratio is equal, males to females (Newsome, 2002; M^{c}Carty, 1993). The onset of RA is usually between 20 and 40 years of age but may occur at

any age. RA is not race or continent specific and affects people of all ages, ethnic and social classes (Farley & Hendry, 2002). RA is classified as a rheumatic disease which also includes Systemic Lupus Erythematosus and Scleroderma. RA is an acquired chronic disease whose etiology is believed to be multifactorial. Factors include host immune response, the environment and possibly infecting agents. The complex interactions of the factors obscures the recognition of a primary causative factor (ARA, 2003).

As mentioned above, RA is a systemic inflammatory disease displaying both articular and, in severe cases, extra-articular manifestations. RA patients may have heart, liver or kidneys complications, particularly when associated with polyarthritis conditions and scleroderma. Articular destruction is the consequence of a chronic cellular immune response in the sublining tissue of the rheumatoid synovial membrane (Tak et al., 1997) The cytology of RA inflamed joint fluid shows a higher-than-normal leukocyte count. In healthy individuals the leukocyte count averages 150/cmm. Leukocytes in inflamed joints are 3-50,000/cmm and in very inflamed joint fluid 50-300,000/cmm or as much as 2000 times the normal number (M^{c}Carty, 1993). Polymorphonuclear leukocytes make up less than 25% of the cells in healthy synovial fluids whereas inflamed joints account for 70%. T cells, macrophages and plasma cells act synergistically with local cells creating a destructive process. It has been hypothesized that some unknown transient exogenous trigger at some time prior to the appearance of the auto-immune disease may activate a sub-set of auto-reactive/auto-immune T or B lymphocytes which are then continually stimulated by auto-antigens with which they cross-react, leading to

persistent auto-immunity. However, studies do not show higher titres for viral antibodies in RA population groups compared to non-RA groups. More research is required in the area of acute RA putatively of a viral origin (Machold et al., 1998; Cassinotti et al., 1995).

Activated T cells (the most abundant cell extracted from the synovial membrane of patients) play a central role in the pathogenic process. Once activated, these cells, together with mononuclear cells and activated synovial A and B cells, locally elaborate a "cascade" of cytokines which are specifically involved as mediators of inflammation and joint destruction. In early RA, the production of Interleukin-1 (IL-1) is increased. Patients with established RA have an increased expression of macrophages and fibroblast-derived factors such as tumour necrosis factor alpha (TNFα) (Feldmann et al., 1996; Arend & Dayer, 1995; Kanik et al., 1996). The presence of plasma cells is also characteristic of the infiltrate seen following the initial acute inflammatory response and is responsible for the extra-vascular immune complex deposition affecting synovial tissue (Muller-Ladner 1997). Several auto-antibodies including Rheumatoid Factor (RF) and anti-collagen antibody are produced by synovial plasma cells, suggesting that local antigens may be involved in both the immune complex formation and lymphocyte activation in the involved tissues (NIH, 1984). RF is an auto-antibody and is a feature of RA which distinguishes it from other arthritises such as osteoarthritis. Blood tests may confirm the presence of RF but a negative result does not preclude a diagnosis of RA (Williams, 1996).

Table 1. Rheumatoid Arthritis Diagnostic Criteria	
1. Morning Stiffness 2. Pain on motion or tenderness in at least one joint 3. Swelling (soft tissue thickening or fluid, not bony overgrowth alone) in at least one joint 4. Swelling of at least one other joint 5. Symmetrical joint swelling with simultaneous involvement of the same joint on both sides of the body 6. Subcutaneous nodules over bony prominences, on extensor surfaces, or in juxta-articular regions 7. Roentgenographic changes typical of rheumatoid arthritis which must include at least bony decalcification localized to or greater around the involved joints (and not just degenerative changes) 8. Positive agglutination (anti-gammaglobulin) test 9. Poor mucin precipitate from synovial fluid (with shreds and cloudy solution) 10. Characteristic histological changes to synovial membrane (fibroblasts advance into bone) 11. Characteristic histological changes in nodules	
Classic	7 of 11
Definite	5 of 11
Probable	3 of 11

1.1 Oral Manifestations of Rheumatoid Arthritis

Rheumatoid diseases have numerous oral manifestations. Individuals with Sjögren's Syndrome, a rheumatic disease, have significantly reduced saliva production. Studies of elder populations classified with reduced saliva flow may attribute the decrease to aging or award a diagnosis of early/mild Sjögren's Syndrome or RA-related diseases rather than to RA directly (Hochberg et al., 1998; Grisius, 2001; Hay et al., 1998). Reduced saliva flow decreases the self-cleansing ability of the mouth increasing food retention in the oral cavity. The retention of cariogenic food particles and decreased buffering capacity associated with reduced saliva flow increases caries risk. Saliva lubricates the oral cavity and facilitates mastication, which may be

difficult in a dry mouth (Garg & Kirsh, 1995). Saliva has anti-fungal and anti-bacterial properties which, when reduced, increases the risk of Candidiasis in rheumatoid patients (Kindelan et al., 1998).

The effects of RA in the mouth are not well documented. Degenerative joint disorders are common in RA populations. Temporomandibular joint (TMJ) dysfunctions such as crepitus with pain, joint tenderness and pain on opening have been verbally reported by 67% of a RA study group as compared to 32% in a non-RA group (Yamakawa et al., 2002). Clinical examination of another RA group which self-reported 33% TMJ dysfunction revealed 40% involvement of the TMJ. Researchers using high resolution computerized tomography (HRCT) determined frequency of involvement was actually 86%. Findings included decreased joint space (33.3%), subchondral cysts (46.6%), and condylar head resorption and/or demineralization (26.6%). HRCT examinations may be beneficial for RA patients prior to the manifestation of clinical symptoms (Bayar et al., 2002).

Lichen planus is a frequent oral sign associated with rheumatoid diseases. Lichen planus is typically linked with Lupus Erythamatosis, a rheumatoid disease, and not linked with RA directly by researchers. The mucosa of RA patients may be thin and have lichenoid lesions which are easily traumatized, or appear normal as compared to the general population (Gonzales-Mole et al., 2003). Lichenoid lesions vary in size, may be painless or sensitive and are prone to causing a burning sensation in the mouths of RA patients (Lozada-Nur et al., 1994; Silverman et al., 1985).

Potentially fragile tissues, decreased saliva, and compromised hand and elbow function may contribute to higher plaque levels due to compromised self care further

increasing risk of oral disease (McMahom, 2002). Most tasks can be performed with 100 degrees of flexion, extension, pronation and supination. A smaller range of motion results negatively in function and creates significant disability, further compromising oral self care (Murphy, 2002).

RA populations have significantly higher numbers of decayed, missing and filled teeth as well as edentulous subjects and subjects with partial fixed or removable dentures. Therapies and procedures directed toward pain reduction and improved motion are the cornerstone of treatment (Heasman & Seymour, 1990; Murphy, 2002).

1.2 Treatment Standards

Rheumatoid Arthritis is a debilitating auto-immune disease. Current treatment modalities attempt to relieve symptoms and suppress the destructive process of the disease. Traditional therapies are directed at pain management and a reduction of pain with the goal of increased mobility and comfort (Murphy, 2002). New generation drug therapies attempt to halt the progression of the disease and associated tissue destruction. Side effects of medications range from mild to severe and vary from diarrhea, increased frequency of cancers, hypertension, liver degradation and osteoporosis. Oral mucosal ulceration and gingival enlargement also occur.

Non-steroidal anti-inflammatory drugs (NSAIDS) are used to control the symptoms of RA but are not effective in slowing or eliminating the destructive disease processes. NSAIDS also cause significant gastrointestinal toxicity including gastro-

duodenal perforations, ulcers and bleeding ulcers (Gaston, 1999). Cyclooxygenase-2 (COX-2) inhibitors celecoxib (Celebrex and Rofecoxib) are new generation NSAIDS. The anti-inflammatory activity of COX-2 is attributed to the inhibition of the production of prostaglandins by host COX-2. COX-1 produced prostaglandins are gastro-protective and are not affected by COX-2 inhibitors, which accounts for COX-2 having fewer gastrointestinal side effects, specifically gastro-duodenal ulcers, than traditional NSAIDs. Rofecoxib has proven to be as effective as Naproxen with less gastrointestinal bleeding and ulcers. However, myocardial infarction and other cardiovascular events occur more frequently with Refecoxib than Naproxen.

The effects of long-term use of COX-2 inhibitors have not been established. Abdominal pain is the most common cause of discontinuation of treatment. Other side effects include myocardial infarction, hypertension and nephrotoxicity. COX-2 causes a decrease in renal function caused by a decrease in renal blood flow. COX-2 not associated with any disease-modifying action and this symptomatic relief may delay more definitive therapy.

Biological response modifiers have recently been developed which attempt to neutralize the important pro-inflammatory cytokine TNFα that is responsible for the production/induction of IL-1 and IL-6 (Bondeson & Maini, 2001). The drugs act as free receptor sites for TNF, thereby preventing/halting the sequence of immune response events which occurs during normal binding. Infliximab (Remicade) is non-antigenic and non-immunogenic. Side effects include upper respiratory infections causing hypertension and death. Patients also experienced fever and chills upon

administration of the injectable drug as well as injection site infections (Kiely & Johnson, 2002; Ferraccioli et al., 2002).

Another biological response modifier used in the treatment of RA is Enbrel (Etanercept), which is a competitive inhibitor of TNF. Enbrel, a diametric form of a TNF receptor, acts as a TNF receptor, binding to TNF receptor sites and leaving the naturally occurring TNF inactive (Bondeson J & Miani RN 2001). Etanercept is as effective as Methotrexate (MTX) in reducing the symptoms, swelling and associated pain of RA and may be used alone or with MTX. Enbrel does, however, stimulate auto-antibody production and should be reserved for patients unresponsive to MTX or other disease-modifying anti-rheumatic drugs (DMARD) (Strand & Cohen, 2001; Bathon et al., 2000). These drugs are recommended to be used in conjunction with methotrexate in order to reduce pain and halt the progession of the disease. Etanercept is effective alone or with MTX but should be reserved for patients unresponsive to MTX alone or other disease-modifying anti-rheumatic drugs (Strand & Cohen, 2001).

Systemic corticosteroids have been one of the mainstays of drug therapy in RA. The glucocorticosteriod Prednisone is used extensively as an anti-inflammatory in the treatment of RA. The precise mechanism of action in RA is not understood. Prednisone inhibits the accumulation of macrophages in inflamed areas and decreases the concentration of immunoglobulin and complement in an area of immune response. The side effects from Prednisone are many and range from weight gain to respiratory failure. The use of Prednisone increases the risk of infections and osteoporosis. RA patients who are long-term users of Prednisone have a shortened

life span. Corticosteroids such as Prednisone have been shown to be effective in halting the progression of the disease process. However, the side effects can be life threatening.

There are numerous medications on the market for the treatment of RA. An ideal medication for the treatment of RA should be effective with low toxicity. Such a medication should reduce symptoms of pain and also halt the progressive destruction of tissues. DMARD impact the progression of RA and reduce pain. Once used only as a last stage drug, use of DMARD is now recommended early on in the disease to prevent progressive and irreversible tissue destruction. The benefits of DMARD must outweigh the toxicities in order to be widely accepted as an effective treatment against RA (Fries, 1999).

Chapter 2: Disease-modifying Anti-rheumatic Drugs

2.1 Methotrexate

Methotrexate (MTX) is a folate antagonist used to treat neoplastic diseases. It is routinely used in chemotherapeutic management of bladder, leukemia, breast, head and neck cancers. MTX is also used as a disease-modifying anti-rheumatic drug to treat psoriasis, scleroderma, systemic lupus (SLS) and rheumatoid arthritis. MTX is considered the treatment standard for aggressive or severe RA patients who do not respond to NSAIDS. MTX is among the most commonly used drugs for the treatment of RA. Pharmacologically MTX is classed as an antimetabolite due to its antagonist effect on folic acid metabolism. Hirsutism and oral ulcers as well as poor wound healing and increased risk of infection are some of the side effects. MTX has been proven to be effective, however, discontinuation of MTX treatment regimens is frequently due to adverse side effects including death (Choi et al., 2002).

2.1.1 Mechanism of Action

Methotrexate has two primary mechanisms of action. The first is the competitive inhibition of the enzyme dihydrofolate reductase (DHFR), the enzyme that reduces folic acid to tetrahydrofolic acid. Tetrahydrofolate must be regenerated by via the DHFR-catalyzed reaction in order to maintain the intracellular pool of tetrahydrofolate one carbon derivatives for purine and thymidylate nucleotide biosynthesis. The inhibition of DHFR by MTX results in a decrease of nucleic acid synthesis. Thus, DNA synthesis, repair and cellular reproduction are inhibited. MTX

is most effective against rapidly reproducing cells, which means it is highly effective against rapidly reproducing malignant tissues. The rapidly reproducing cells of bone marrow, buccal, intestinal mucosa and fetal tissue may also be adversely affected (Cronstein et al., 1993).

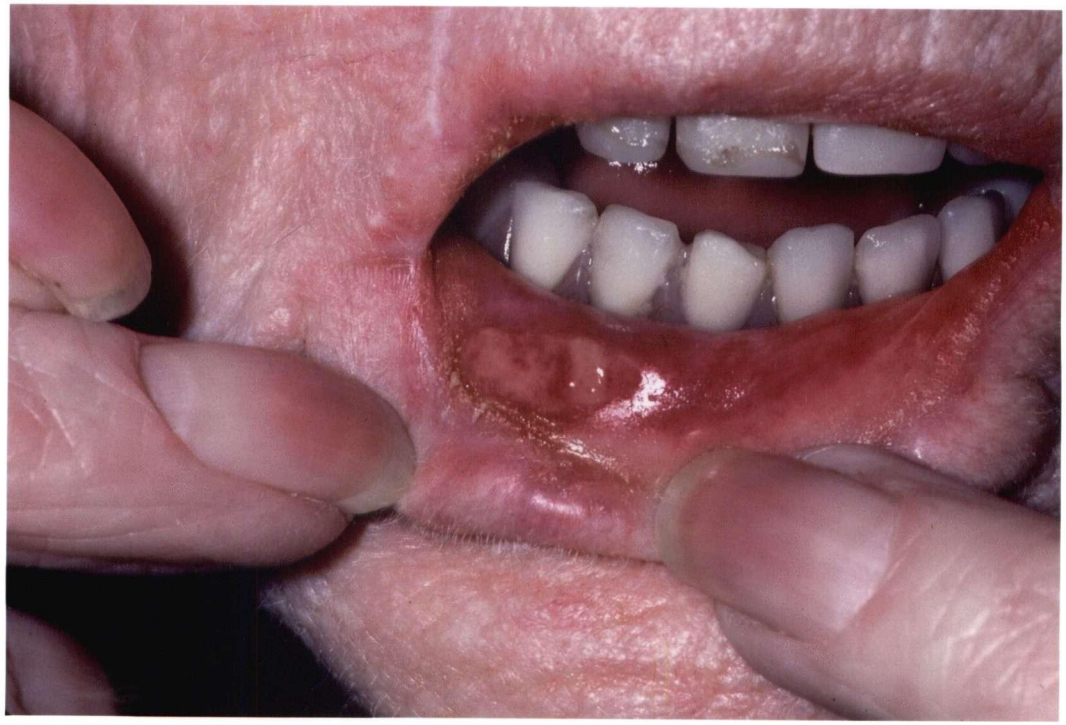
The second primary mechanism of action of MTX is as an immunosuppressive agent. The exact mechanisms in RA patients are unknown but are thought to relate to immunosuppressive activity. It has been proposed that MTX inhibits the enzyme 5-aminomidazole-4-carboxamide ribonucleotide transformylase which precipitates a complex sequence that results in the release of adenosine and the stimulation of an anti-inflammatory signal. Increased intracellular levels of 5-aminomidazole-4-carboxamide ribonucleotide in RA patients supports this theory. The side effects of MTX can be severe. They include elevated liver enzymes and cirrhosis of the liver (29%), leukopenia, thrombocytopenia and renal dysfunction. Despite its life threatening side effects, MTX is the first line drug choice of rheumatologists for the treatment of aggressive RA in the United States (78%) and Canada (68 %) (Maetzel et al., 1998).

2.1.2 Oral Side Effects

Ulcerative stomatitis is one of the most commonly reported side effects of methotrexate. The rapidly reproducing cells of the oral mucosa are sensitive to methotrexate which targets such cells. The occurrence of ulcerative stomatitis ranges from 36-83% in RA patients taking MTX. Lesions are slow to heal and painful (Figure 1). Stomatitis can result in the discontinuation of treatment, resulting in

disease progression. Patients with a previous history of stomatitis have an increased risk for the incidence and severity of stomatitis while on MTX (Carpenter et al., 1997). Cancer patients on MTX have demonstrated an increase in herpes simplex infection. Studies with RA patients have not supported the use of prophylactic anti-virals due to a low incidence of herpes infections.

Figure 1: Methotrexate Ulcerative Stomatitis at 34 Days
Methotrexate associated ulcerative stomatitis is severe and slow to heal



2.2 Cyclosporin

Cyclosporin (CYA) is potent disease-modifying agent. It is derived from fungi and was originally developed as an antibiotic. CYA is a cyclic polypeptide produced by the metabolism of two fungi, Trichoderma polysporum and Cylindrocarpum lucidum. It is an effective immunosuppressive agent used widely in organ transplant

patients. It differs from other immunosuppressive agents because it does not cause a generalized inhibition of cell proliferation. (Kay & Benzie, 1983).

CYA is known to be an effective disease-modifying anti-rheumatic agent. It is also used in the treatment of severe or rapidly progressive rheumatoid arthritis cases that are unresponsive to other treatment regimes. CYA has proven to be effective in reducing joint inflammation at doses up to 5 mg/km/day. Nephrotoxicity is also a problem in RA patients, resulting in discontinuation of treatment (Feutren & Mihatsch, 1992). Lower dosages of 3.8-5 mg/kg/day with serum levels of 150 ng/ml are still effective and have decreased adverse renal dysfunction (Tugwell et al., 1990). Side effects in transplant patients include nephro and hepatotoxicity, onogenicity, hypertension, hirsutism, gastrointestinal upset and gingival hyperplasia. Gingival overgrowth as a side effect of CYA was reported in 1979 in renal transplant patients (Borel, 1979). The most common reasons for cessation of CYA therapy is increased renal dysfunction and elevated blood pressure (Kvien et al, 2002). Side effects also occur when CYA is used to treat auto-immune diseases such as systemic lupus erythematosus, psoriasis and sclererderma (Britton & Palacios, 1982). In addition to nephrotoxicity, early studies indicate gastrointestinal intolerance is stated as a significant side effect in RA patients on CYA. It is speculated that the higher incidence of gastrointestinal side effects in RA patients compared to non-RA is likely due to the past concomitant use of NSAIDs (Van Rijhoven et al., 1986). Gingival overgrowth as a side effect of CYA was first observed in renal transplant patients (Borel & Gunn, 1986).

2.2.1 Mechanism of Action

The mechanisms involved in the action of CYA are not clearly understood. It has a narrow therapeutic range. CYA is bio-transformed to approximately 15 metabolites and then the response in humans is not well understood. There is not one singular metabolic pathway and patients show variations in responses to CYA. In early mouse studies, CYA demonstrated inhibition of early stages of T lymphocyte activation. Mouse splenic lymphocytes were more sensitive to inhibition by CYA than the activation by the B lymphocyte mitogen lipopolysaccharide (LPS), which gave evidence that the effects of CYA on humoral immunity were secondary to inhibition of T-helper cells (Wiesinger & Borel, 1979). Later in vitro studies showed that the sensitivity depended on the specific mitogen used. Subsequent in vivo studies supported the theory that CYA selectively suppresses sub-populations of T-lymphoctyes with only certain subpopulations of T and B lymphocytes showing sensitivity to CYA, with both cellular and humoral immunological responses inhibited (Britton & Palacios, 1982). T suppressor cells are relatively resistant to CYA. The activation by antigen of both T helper and T cytotoxic cells is inhibited by CYA which is not cytotoxic to lymphocytes, and its effects on lymphocyte activity is reversible upon cessation of the drug. However, CYA has been shown to cause inhibition of the rate of protein synthesis in unstimulated lymphocytes (Kay & Benzie, 1983). In pigs, CYA inhibits an early step in lymphocyte proliferation prior to the initiation of DNA synthesis.

The main therapeutic effect of CYA is on the cellular immune system suppressing the function of the T-helper cells. CYA interrupts the synthesis of most

lymphokines, including IL-2 and gamma interferon by T lymphocytes. Ongoing synthesis of IL-2 is also affected. Studies of asthmatic patients on 5 mg/kg/day have shown a marked reduction in T lymphocytes with IL-2 receptors, a marker for T cell activation (Fukuda et al., 1995). T-suppresser cells seem immune to the influence of CYA. In an immune response, lymphokines mediate the activation of macrophages and cytotoxic T lymphocytes, which have a direct lytic effect on the foreign cell (Kjeldsen et al., 1993). IL-1 releasing cytokines are involved in the inflammatory process which stimulates T cells and fibroblast production. Lymphokines also activate B lymphocytes that produce specific antibodies against the antigen exposed by foreign cells such as a transplanted organ. CYA has little effect on B-cell mediated antibody production (Borel & Gunn, 1986; Herold et al., 1986). The major effect of the drug is to suppress the production and function of lymphocytes, primarily the T helper cells. This affects the T cell activity and the synthesis of IL-1 and the T cell becomes unresponsive to IL-1 and interferes with the formation of IL-2 (Herold et al., 1986; Borel & Gunn, 1986).

In vitro, CYA inhibits lymphokine synthesis, transcription of IL-2 and gamma interferon by preventing the recognition of the antigen as "non-self". In vivo, CYA facilitates a complex series of activities including its ability to bind to macrophages and inhibiting the secretion of IL-1. The action of CYA is not indiscriminate and does not affect the entire immune system. At therapeutic doses, CYA modifies the action of T lymphocytes on the B lymphocytes and consequently has some effect on humoral immunity without affecting B-memory cells and antibody production. This creates a selective immunity in patients. Although the exact mechanism for the

inhibition is not clear, studies have shown that a Ca^{2+} signal is required in normal lymphocyte function which increases Ca^{2+} concentrations by releasing Ca^{2+} from intercellular stores. There is evidence that CYA binds to calmodulin, the protein that mediates the Ca^{2+} signal. CYA may inhibit T and B lymphocyte proliferation by antagonizing the Ca^{2+} signal. The Ca^{2+} signal is essential for the induction of the synthesis of the mRNA for IL-2 and other lymphokines. CYA blocks lymphocyte activation at one or more Ca^{2+} dependent steps (Hess & Colombani, 1987). The exact mechanism or step is not known. Current research is exploring evidence that IL-10 and IL-6 are higher in non-medicated RA patients than non-RA population groups. IL-10 is a B-cell stimulator and levels are reduced in RA patients on CYA (Ferraccioli et al., 1998). Numerous studies are investigating possible mechanisms for the action of CYA on the suppression of IL-10. The mechanisms by which CYA creates immunosuppression are not clearly understood and are under ongoing investigation by researchers.

2.2.2 Oral Side Effects

Three major drug categories are associated with Gingival Overgrowth (GO): anti-convulsants, calcium channel blockers and cyclosporin. Incidence and prevalence studies demonstrate wide variability in gingival responses to these medications (Steele 1994). Differences within study populations, including differences in age and gender of patients, dose and duration of drug use, overall health of patients, and local factors, create a number of confounding variables. RA is a confounding variable with an unpredictable response (Dongari et al., 1993). Gingival enlargement

can occur as a side effect of these medications. Originally referred to as gingival hyperplasia, histological examination of tissues from CYA patients show that the tissues are not hyperplastic (Barber et al., 1992). The more accurate term "gingival overgrowth" refers to histological examination of Phenytoin-induced gingival enlargement, which showed that the tissues were an over-accumulation of normal tissue cells resulting in a fibrosis caused by an accumulation of collagen fiber bundles, not an overgrowth of fibroblasts as originally thought (Hassel et al., 1984). The etiology of drug-induced tissue enlargement varies. The term gingival overgrowth (GO) was used in this study.

Phenytoin, an anti-convulsant, was one of the first medications recognized to cause GO. Used by over three million North Americans, phenytoin causes GO in approximately 50% of daily users (Jones JE 1988). The impact of GO on patients has been well documented in the phenytoin literature and has been the standard for the development of GO indices. Recognition of GO in patients using calcium channel blockers in addition to recognized GO-inducing medications resulted in modification of indices and the development of additional assessment tools (Pernu et al., 1993). GO increases tissue irregularities and subsequently increases accumulation of food debris and plaque. Secondary inflammation as a result of increased plaque accumulation may increase patient discomfort. Loss of function may occur when severe GO interferes with mastication and normal speech. Esthetics may also be impacted negatively (Rostock et al., 1985).

GO is usually initiated in the interdental papilla and may spread to marginal and attached gingival tissue. Phenytoin GO is often fibrotic and light pink. Calcium

channel blockers such as nifedipine initiate GO that is more vascular in nature with increased friability. GO occurs on the anterior teeth with the labial surface affected more often than the lingual (Somacarrera et al., 1994a).

Gingival attachment levels are usually not affected and an increase in probing depth occurs from increased tissue mass on the clinical crown. Drug-induced GO is frequently linked to poor plaque control and/or drug dosages (Steinberg & Steinberg, 1982; Philstrom, 1980).

Studies on the oral side effects of CYA have produced conflicting results. Gingival enlargement was first reported in 1979 in renal transplant patients (Borel, 1986). CYA is used in treating life threatening illnesses or conditions in relatively small populations. Consequently study populations are usually small with many variables (Table 2). CYA-induced study results rarely reflect the impact of age, gender or other systemic factors involved.

Table 2: Population Sizes in CYA Studies

Investigator	**Year**	**Medical Condition**	**Number of CYA Participants**
Daly	1992	renal transplant	1
Ferraccioli	1998	RA	8
Hefti	1994	MS	40
King	1993	renal transplant	18
Mariani	1993	renal transplant	8
Niimi	1990	renal transplant	8
O'Valle	1995	renal transplant	21
Pernu	1992	renal transplant	22 (9 Ca blocker, 13 corticosteriods

Histological examinations of CYA GO have shown there are many fibroblasts in CYA GO, with a particular abundance of amorphous substance and a marked plasma cell infiltration with marked development of rough endoplasmic reticulm, Golgi apparatus and plasmatic granules. There is an increase in cytoplasmic volume of

individual fibroblasts with increased collagen and connective tissue matrix (M^{c}Gaw & Porter, 1988). Early examinations considered that high numbers of fibroblasts may indicate a hyperplasia while more recent histological examinations do not support an increase in the number of fibroblasts. This may be due to biopsy samples viewing an evolutionary stage of GO with changes in fibroblasts density occurring as the lesion ages, but nonetheless gives evidence that CYA GO is not true a hyperplasia (Wysocki et al., 1983; Rostock et al., 1985; Pan et al., 1992). The GO associated with renal transplant patients on CYA has plasma cells at the gingival level but this may be due to the individual's sensitivity to the drug or one of its metabolites, allowing a reaction which is favored by lymphokine inhibition.

In vitro studies showed that CYA induced a proliferation of fibroblasts but these fibroblasts were not stimulated to synthesize DNA. With no remarkable increase in proliferation in culture, the statement that lesions are not hyperplastic in nature is supported (Barbar et al., 1992).

Other in vitro studies suggest another mechanism for CYA-induced GO. Elevated levels of keratinocyte growth factor (KGF) were found in in vitro tissue samples in CYA-induced GO, which produced the hypothesis that KGF receptors (KGFR) may be up-regulated in CYA-induced GO (Das et al., 2002). In healthy tissue, KGFR were not found in basal and cornified cell layers of the inner and outer layers of epithelium, respectively. In contrast, KGFR were found in basal as well as granular cell layers of CYA GO tissue samples (Kvien et al., 2002). KGF stimulates TGFβ which is actively involved in connective tissue production. This may indicate a hyperplastic growth in CYA GO.

The initiation of the GO in CYA patients is not clearly understood. The link between phenytoin GO and plaque has been well documented (Hassell et al., 1984; Lundstrom et al., 1982). Early studies identified a significant correlation between plaque and GO. Studies supporting a similar etiology for CYA GO abound (Seymour & Smith, 1991; M^{c}Gaw et al., 1987; Somacarrera et al., 1994a). Cases studies considered CYA a co-factor with gingival inflammation and plaque in the development of GO (Rateitschak-Pluss et al., 1983).

Animal studies which stimulated GO in ferrets on CYA strengthened the evidence of plaque as a causative factor in CYA GO (Fischer et al., 1996). However, more current studies, and even an early study, questioned whether plaque was a causative factor or if increased plaque levels in patients with GO were a result of accumulation around plaque retentive tissue irregularities (M^{c}Gaw et al., 1987; Seymour, 1991).

The effects of oral hygiene and plaque removal on CYA GO is not definitive. Researchers found plaque control reduced inflammation but did not reduce GO or prevent it (Seymour, 1991; Somacarrera et al., 1994b). Research in a study with 27 renal patients being treated with CYA showed that plaque control did not significantly prevent GO but may be of some benefit in reducing gingival inflammation. Significant GO occurred in both CYA and control groups.

This study gave rise to the hypothesis that age may be a factor. Older patients demonstrated more GO than younger patients and therefore may be more susceptible to developing GO. GO was not simply a plaque-related or drug-related manifestation.

This hypothesis was not supported by studies of Type I diabetes patients treated with CYA who demonstrated greater risk in childhood and adolescence than adulthood (Daley et al., 1986). The degree of plaque was not as significant as the presence of plaque in the presence of GO in Type I diabetes patients or transplant patients (Daley et al., 1986; Pan et al., 1992).

After it was established that the degree of plaque and the age of the patients was not a factor, researchers examined the effects of dose on the occurrence and severity of GO. Again animal studies produced good evidence of a strong relationship between dose and GO (Fu et al., 1995). Rats given 450 mg/day developed GO. However, human studies did not support a significant relationship between dose and GO (Thomason et al., 1993; King & Fullinfaw, 1993). Extensive research on kidney transplant patients receiving standard maintenance doses of 3.2-4.5 mg/kg/day revealed no correlation between dose, blood level, or plaque (Silness & Loe, 1964) in non-responders and CYA responders who developed GO (King & Fullinfaw, 1993; Seymour& Smith, 1991; Thomason et al., 1993). Current transplant treatment regimes initiate CYA therapy prior to transplantation, which avoids the need for high dosages in the first weeks after surgery (Romanos et al., 1992; Matas et al., 1988). Mean dosages of 300 mg/day are comparable to mean dosages of RA patients (Darbar et al., 1996). Duration of treatment has not proven to be a predictor of GO in studies. Cross-sectional studies examining the anterior twelve teeth of renal transplant patients on CYA showed that the only significant variables were gingival inflammation and time. GO was less likely to be present the longer the individual had been on the medication (Montebugnoli et al., 1996).

One of the common side effects of CYA therapy is hypertension. Calcium channel blockers, especially nifedipine, were traditionally used to control hypertension associated with compromised renal function or renal dysfunction. Diabetes patients on CYA and nifedipine who received scaling and root planing with ongoing meticulous plaque control had significant improvement in GO (Hancock & Swan, 1992). Plaque was also strongly correlated with GO in heart and renal transplant patients treated with nifedipine and CYA (Nishikawa et al., 1991; Thomason et al., 1993). These studies also firmly established that calcium channel blockers exacerbated GO in CYA patients. CYA GO in patients also taking nifedipine is more vascular than GO from CYA alone (Barak et al., 1987). When nifedipine was replaced with an alternative hypertension medication, GO was significantly reduced (Pernu et al., 1993; O'Valle et al., 1995; Thomason et al., 1993). This suggests that CYA GO is not initiated by plaque but is multifactorial and confirms individual patient variability in gingival response to the drug.

In a renal transplant case studies, improvement in oral hygiene reduced inflammation and tenderness but did not reduce GO. However, a reduction in the CYA dose from 400 mg/day to 200 mg/day did result in a reduction of GO (Daly, 1992; Rostock et al., 1985). However, these patients had significant compounding factors specifically a liver transplant, Hepatitis B and/or Hepatitis C.

Renal transplant patients had an initial decrease in GO after periodontal therapy but those patients on a combination of CYA and dihydropyridine were at risk for reoccurrence or progression (Pernu et al., 1993). These findings led to the hypothesis that plaque itself was not a significant factor but was a reservoir for the retention of

CYA. CYA levels were found to be 12 times higher in whole saliva than pure submandibular or parotid gland saliva, leading researchers to believe that plaque acts as a reservoir for CYA. Studies that showed serum levels of CYA were low and were never exceeded by salivary levels strengthened the evidence for plaque as a causative factor in GO (Niimi et al., 1990). Subsequent studies confirmed that blood levels of CYA were exceeded by the levels of CYA in plaque (M^{c}Gaw et al., 1987; King & Fullinfaw, 1993).

However, when researchers evaluated effects of frequent prophylaxis and oral hygiene instruction (OHI) over a six month period plaque was not related to GO. Despite an intensive professional debridement regime resulting in decreased plaque and inflammation levels, the difference in GO was small. Overgrowth increased in both the treated and non-treated study groups (Seymour and Smith, 1991). Cyclosporin gingival overgrowth in 18 renal transplant patients taking CYA for a minimum of three months was not related to plaque as recorded using the Silness & Loe Plaque Index (1964). There was no correlation between GO and age, gender, dose, blood levels or saliva levels between responders and non-responders. Dosages of 3.2-4.5 mg/kg were used in the study. It was concluded that the degree of GO was not related to plaque or dependent on pharmacokinetic variables or amount administered but on individual sensitivity and ability to metabolize the drug (King & Fullinfaw, 1993).

The severity of GO has been measured using primarily two indices. The Phenytoin Gingival Inflammation Index (PGII) (Hassell et al., 1984) which assesses colour, tone and bleeding and the Hyperplasia Index (Angelopoulos & Goaz, 1972) which

scores 0 as normal, 1 as mild with blunting of interdental papilla, 2 as moderate with GO extending up to one third of the crown, and 3 as severe extending over 2/3 of the crown or affecting the attached gingiva (Seymour & Smith, 1991; Pernu et al., 1993; Hefti et al., 1994; Montebugnoli et al., 1996). The modified HI index included thickening of marginal gingiva or lobular granulation of the gingival pocket or overgrowth less than one third of the tooth in a score of "1"; a score of "2" included moderate gingival overgrowth extending to the middle of the tooth; and severe gingival overgrowth covering up to two thirds of the crown or the whole attached gingiva was given a score of "3" (Pernu & Pernu, 1992). Other researchers made alternate modifications to the index to measure the vertical component of GO. Separate scores of "0" indicating normal width of free gingival margin; "1" thickening up to 2 mm; and "2" thickening greater than 2 mm were also assigned (King & Fullifaw, 1993).

In the studies where plaque scores were included, two indices were used: the Silness & Loe Plaque Index (Montebugnoli et al., 1996; King & Fullifaw, 1993; Seymour & Smith, 1991; Thomason et al., 1993) and the O'Leary Plaque Index (O'Valle et al., 1995; Hefti et al., 1994). Studies with heart transplant patients on CYA therapy reported 60-65% of patients demonstrating GO (Somacarrera et al, 1994a; Pan et al., 1992). However, the severity of CYA GO is not always clearly stated. Only 20% of the patients in these studies demonstrated a GO score of 2 or 3, moderate or severe respectively.

Dihydropyridine (DHP) in combination with CYA produced significant increases in GO in a study of 27 renal transplant patients. CYA alone produced only scores of

"1" or GO which is mild with blunting of papilla, while the combination group showed 50% of the patients scoring "2" or "3", with "2" being moderate extending to the middle one-third of the tooth and "3" indicating severe overgrowth covering two-thirds of tooth or affecting the whole of the attached gingiva. The CYA group of 14 patients had less overgrowth at re-examination after periodontal therapy while the combination group of 13 patients had more GO. The researchers concluded that the combined effects of CYA and DHP medications may be so strong as to overcome the effect of reduced gingival inflammation from periodontal therapy/gingivectomy (Pernu et al., 1993).

GO decreased over the duration of CYA therapy in heart transplant patients. Of the 39 patients, 11 showed some evidence of GO. The degree of oral hygiene did not relate to GO. Only one of the 18 patients on CYA for more than 36 months showed signs of GO while 10 of the 21 patients on CYA for less than 36 months showed GO. This study could not verify if gingival inflammation was the cause of 28% of patients demonstrating GO or a consequence of GO. The amount of oral hygiene was not related to GO (Montibugnoli et al., 1996). Other studies have reported 49% and 59% prevalence of significant GO (King & Fullinfaw, 1993; Hefti, 1994). Additional studies found significant GO in renal patients treated with CYA. A study of 22 renal patients on CYA or CYA and nifedipine reported a 77% occurrence of significant GO. However, 11 out of 22 patients treated with CYA were also were treated with nifedipine, with only one patient or 5% having a score of 2 or 3. They found that CYA-induced GO occurs within the first 3-6 months of treatment and plateaus in the subsequent 9-12 months (Pernu & Pernu, 1992; Seibel et al., 1989).

CYA is an effective DMARD in therapeutic doses. The exact mechanism of action is not clearly understood and the mechanisms by which it causes gingival overgrowth is not known. The prevalence of GO varies significantly in study results and is influenced by the combined use of GO-inducing drugs.

2.3 Summary

New therapies attempt to halt the progression of RA disease, not just treat its symptoms. RA patients suffer from pain, increasing disability, decreasing quality of life and social isolation despite what physicians consider effective treatment drugs (Machold et al., 1998). Studies of RA populations report that the work attendance of 62% of RA patients is negatively affected, with 55% unable to work at all and an additional 13% working a reduced work schedule (Doeglas et al., 1995). The impact of RA is a substantial cost to society in lost productivity and cost of treatment (Lee & Weinblatt, 2001). Poor functional status is a powerful predictor of mortality with RA patients. Patients with increased dysfunction have higher mortality rates (Soderlin et al., 1998).

Self-reporting tools used by RA patients provide researchers with valuable data on pain levels and loss of function. Self-assessment scales are effective in evaluating the efficacy of therapies and the financial benefits of expensive drug therapies and future treatment modalities (Lubeck, 2002: Dickerson and Fischer, 1995). The trend is increased use of DMARDs and DMARDs in conjunction with NSAIDs despite evidence that combination therapy increases toxicity (Ward & Fries, 1998).

Cyclosporin is a potent disease-modifying agent that is effective in modifying disease progression and immunological responses. Unlike NSAIDs, which suppress and relieve symptoms only, CYA is capable of halting the progression of the disease and continued degradation of tissues. In addition to the severe side effect nephrotoxicity, one of the debilitating side effects of CYA is gingival overgrowth. Used primarily as a transplant anti-rejection drug, the transplant literature shows a high occurrence of the oral side effect, gingival enlargement, associated with the use of cyclosporin. Gingival enlargement usually arises in the anterior interdental regions and may be limited in size and location or may become more generalized and severe in nature (Dahllof et al., 1992: Jones et al., 1988: Penarrocha-Diago et al., 1990). CYA-induced GO is more pronounced on the labial than lingual surfaces of affected gingival (Tyldesley & Rotter, 1984). The degree of GO has been related to dose, duration and plasma levels but the majority of studies do not support this correlation (Dahloff .& Modeer, 1986; Penarrocha-Diago et al., 1990)

CYA GO generally begins in the anterior of the mouth within 1-3 months (Seymour & Jacobs, 1992). The role of CYA in promoting the development of GO is unclear. Primarily used in transplantation immunosuppression, CYA's effect on GO in patients with rheumatoid arthritis is unknown. Previous studies have had conflicting results as to the relationship between plaque and the development of GO. The incidence of cyclosporin-induced GO varies between studies (Dongari et al., 1993; Seymour & Jacobs, 1992).

The purpose of this study was to determine the prevalence of gingival enlargement in individuals with RA being treated with the immuno-suppressive medication

cyclosporin. RA patients who had begun participation in an initial trial of the drug had not received oral assessments prior to initiation of therapy. Oral manifestations of RA are not well documented in the literature. Physicians and nursing staff involved in the clinical drug trial felt that, with compromised hand function and associated challenges with plaque control, the RA patients with their unique immune response may be at greater risk for GO and oral side effects than transplant study populations reported in the research literature. RA patients are routinely treated with Methotrexate (MTX), a folic acid antagonist, which causes severe oral ulcerations. RA patients on MTX are slow to heal and at greater risk for infection than RA patients on non-steroidal anti-inflammatory drug (NSAID) regimes. NSAIDs are used to control pain but do not modify the disease or to affect the destructive disease process.

It was felt by the investigator that, because of the unique immune response in the RA study population, a longitudinal study was required to determine the time frame in which drug treatment patients were most at risk and the prevalence and severity of GO as a side effect of CYA use.

2.4 Research Question

Does plaque, as measured by the Silness & Loe and the O'Leary Plaque Indices, cause gingival enlargement in rheumatoid arthritis patients on cyclosporin? The relationship between plaque scores and the prevalence and severity of gingival overgrowth will be investigated.

CHAPTER 3: Methods and Materials

3.1 Study Participants

Study participants were recruited from the Mary Pack Arthritis Centre Cyclosporin Clinic in Vancouver on a voluntary basis. Study participants were examined for a period of six months in order to determine the prevalence of GO and the time parameters when patients are most vulnerable for developing GO. Participants in the cyclosporin drug trial were individuals identified as having aggressive and severe RA and being unresponsive to standard treatment regimes. At the time of this study cyclosporin was not approved for treatment of RA. It was identified by the medical staff at the Mary Pack Arthritis Center that the disease of numerous patients was not being successfully managed. Patients with severe and aggressive RA and who were unresponsive to standard treatments did not have a treatment alternative. Patients were permitted to receive CYA through the Emergency Drug Release Program (EDR) of the Canadian Federal Government's Health Protection Branch. At the time of the research there was only one Drug Monitoring Clinic in Canada permitted to use this regime for rheumatic disease patients. Cyclosporin had not been approved in the United States for treating rheumatic diseases.

Patients were monitored for high blood pressure and renal dysfunction throughout the study. Patients with a diastolic pressure greater than 95 mm Hg or renal dysfunction evidenced by serum creatinine levels greater than 30% over baseline were withdrawn from the study. Edentulous patients and patients who were taking a

combination of methotrexate and CYA or calcium channel blockers were excluded from the study.

3.2 Patient Examination

Gingival enlargement usually occurs in the anterior interdental regions and may be limited in size and location or become generalized and severe. GO in the treatment of RA is not well documented. The literature on drug-induced GO is more comprehensive on patients treated with calcium channel blockers, anti-epileptic drugs and CYA used in transplant patients. Examination of the twelve anterior teeth is the standard for GO observation. RA patients have a unique immune system compared to these patients, so to increase reliability, an extended oral examination is appropriate (Rams et al., 1993). GO most frequently occurs in the anterior region (Dahllof et al., 1992; Jones et al., 1988; Penarrocha-Diago et al, 1990). In a previous prospective study of RA patients taking CYA, the buccal surface of a mandibular molar tooth was the only surface to present with mild GO. In this study we chose to include all anterior teeth and the first molar in the examination. If the first molar was not present, the second molar was included.

Patients were examined at the Mary Pack Arthritis Centre in Vancouver in a patient assessment room. A portable dental chair and a standard floor-based dental light were used for each examination. Intra-oral photographs were taken using Kodak Kodachrome 64, 35 mm colour film.

Maximum opening and recession were recorded at baseline and each subsequent examination. Periodontal probing depths were measured to the nearest millimeter using a colour-coded Hu-Friedy probe with demarcations of 3, 6, 9, and 12 mm. All

measurements were taken from the crest of the gingival margin to the sulcus depth at six points around each tooth: buccal-mesial, buccal-mid-point, buccal-distal, lingual-mesial, lingual-mid-point, and lingual-distal.

Gingival recession was recorded from the cementoenamel junction (CEJ) to the crest of the GM at the same six points. Surfaces having cervical restorations were noted (Thomason et al., 1993). To clearly establish the clinical crown, the CEJ to sulcus depth was also recorded on patients with recession. This assisted the investigator in determining the presence of gingival enlargement or increased sulcus depth.

Patients were examined at Day Zero prior to or on the first day of initiation of the drug treatment regime. All data and indices were recorded including the Arthritis Hand Function Test (AHFT) and the Oral Health Impact Profile (OHIP) which were not included in this study. Patients were re-examined every 4-6 weeks for six months. GO most frequently occurs in the first three months of CYA treatment (Dahllof et al., 1992; Jones et al., 1988; Penarrocha-Diago et al., 1990). All data was collected by one clinical examiner who was blinded to the drug trial group being examined. In a previous observational study the examiner had been calibrated to a 95% reliability in assessing GO, plaque and PGII with other examiners in that study.

3.3 Plaque Indices

Plaque plays an important role in gingival inflammation and enlargement (Shibley et al., 1995). Plaque has been linked to the development of GO in patients on CYA. It was therefore important to assess the relationship between plaque and the incidence and severity of GO in this RA patient pool. Plaque indices vary in their intent to assess the presence of plaque or the quality of plaque present. Some indices such as

the Navy Index of Hancock and Wirthlin are regarded as weak in identifying subtle changes in plaque development. It also scores occlusal surfaces that are not of interest in this study but would be in studies of oral hygiene effectiveness. Each index is useful in a variety of applications dependent on the purpose of the study and the use of more than one is sometimes beneficial (Ainamo & Bay, 1975). It was decided that the use of two indices would provide a more comprehensive assessment of plaque for this study. The selected indices have been used extensively in CYA GO research: the Silness & Loe (Seymour, 1991; King & Fullinfaw,1993) and the O'Leary (Hefti et al., 1994; O'Valle et al., 1995; Somacarrera et al., 1994a).

The O'Leary Plaque Index is used to establish only the presence of plaque (O'Leary et al., 1972). Extent of plaque is not reflected in this index and there is no qualitative or quantitative measurement to this index (Table 3). The plaque is scored by examining the study teeth for visible plaque. The plaque is recorded as present or absent without qualifiers. The number of assessment points on the tooth surfaces with plaque present is multiplied by 100 and divided by the number of assessment points scored in the examination. The resulting score is expressed as a percentage of surfaces with plaque. A score of 10% or less is considered good oral hygiene.

Table 3: O'Leary Plaque Index

$$\frac{\text{Total Number of Surfaces with Plaque}}{\text{Number of Teeth Present X 6}} \times 100 = \%\ \text{score}$$

The Silness & Loe Index was recorded after the O'Leary to determine if the degree of plaque was a factor in the development of GO. The Silness & Loe Plaque Index (Table 4) measures the amount of plaque present (Silness & Loe, 1964). Each tooth

is dried and examined for plaque. A probe is used to determine the amount of plaque present. The probe is moved across the tooth at the gingival margin and examined at each of the six assessment points. If there is no plaque on the probe, the tooth is considered plaque free with a score of "0". If the plaque is not visible but is visible on the probe after the probe is moved over the tooth surface, a score of "1" is given. Plaque visible to the naked eye is scored "2" and heavy accumulation filling the gingival crevices is scored "3". Scores are added and divided by the number of surfaces for a score of 0-3. The nominal scale awards a rating of "Excellent" oral hygiene for a score of "0", "Good" for a score of 0.1-0.9, "Fair" for 1.0-1.9, and "Poor" for 2.0-3.0.

Table 4 Silness & Loe Plaque Index

Score
0 = Gingival area of tooth is free of plaque; the surface is tested by running a probe across tooth surface. If no material adheres, the surface is considered plaque free.
1 = No plaque observed in situ with the unaided eye, but plaque is made visible on the point of a probe after the probe is moved over the tooth surface at the entrance to the gingival crevice.
2 = Gingival area is covered by a thin to moderately thick layer of plaque visible to the naked eye.
3 = Heavy accumulation of soft matter, the thickness of which fills the crevice produced by the gingival margin and the tooth surface.

Rating	**Scores**
Excellent	0
Good	0.1-0.9
Fair	1.0-1.9
Poor	2.0-3.0

The Silness & Loe Plaque Index measures the thickness of the plaque but does not evaluate the advancement of the plaque towards the incisal surfaces. This was appropriate for this study group as we anticipated at least a minimal level of oral

hygiene. Routine tooth brushing may be effective on the flat coronal surfaces of the teeth with plaque remaining in the gingival areas. The presence of plaque in contact with tissues is of greater interest than the effectiveness of tooth brushing on coronal areas. Plaque scores were recorded at each appointment. Participants did not receive oral hygiene instruction. Disclosing agents were not used in order to facilitate assessment of gingival inflammation and probing depths. Plaque was recorded at six points on each tooth: buccal-mesial, buccal-mid-point, buccal-distal, lingual-mesial, lingual-mid-point, and lingual-distal.

3.4 Gingival Inflammation Index

Gingival inflammation (GI) is strongly correlated with GO in the Cyclosporin literature. Bleeding is a parameter by which the presence of GI is determined. Bleeding may not be a predictor of periodontal disease activity but is accepted as a indicator of gingival inflammation (Chaves et al., 1993). Prior to evidence of bleeding, gingival changes may be identified such as colour and contour (Bollmer et al., 1986).

Some indices record changes in colour, tone and bleeding in a single score (Silness & Loe, 1964). This is a reliable method for determining tissue changes in a non-GO population. Increased tissue masses due to enlargement may obscure bleeding and tissue responses may not correspond to those anticipated in a general population. A gingival inflammation index was selected that assessed all three aspects of gingival inflammation (colour, tone and bleeding) individually.

The Phenytoin Gingival Inflammation Index (PGII) (Hassell et al., 1984) is a well-validated tool for assessing tissue changes, examining colour, tone and bleeding on

separate scales of 0-2 (Table 5). Colour is assessed on a three point scale with "0" being no clinical reddening; "1" areas of reddening of papillary or marginal tissue; "2" generalized or extreme reddening or cyanotic appearance. Tone scores "0" for firm resilient tissue, "1" for slightly edematous, and "2" for moderate to severe edema and/or tissue friability. Bleeding is assessed with paper points: "0" no bleeding, "1" blood on the tip of paper point and "2" clinically evident bleeding from the sulcus marginal gingiva or papilla after insertion.

Table 5 Phenytoin Gingival Inflammation Index
Colour Scores 0 = no clinical reddening 1 = areas of reddening of papillary or marginal tissue 2 = generalized or extreme reddening or cyanotic appearance Tone scores 0 = firm resilient tissue 1 = slightly edematous 2 = moderate to severe edema and/or tissue friability Bleeding 0 = no bleeding 1 = blood on the tip of paper point 2 = clinically evident bleeding from the sulcus marginal gingiva or papilla after insertion

Tissues were examined at each appointment every 4-6 weeks. Changes in tissue contour, colour and bleeding were recorded.

3.5 Gingival Overgrowth Index

Two indices have been most frequently used to assess gingival overgrowth: the Hyperplastic Index (Table 6) and the Gingival Overgrowth Index (Table 8). The Hyperplastic Index originally used in phenytoin research (Conrad et al., 1974) assesses GO in the horizontal dimension only. Tissues are examined for the presence

of blunting or enlargement and scored on a four point scale (see Table 6) (Pernu et al., 1993; Pan et al., 1992; M^{c}Gaw et al., 1987).

Table 6 The Hyperplastic Index
Score 0 = no gingival overgrowth or enlargement 1 = mild hyperplasia defined as blunting of the papilla 2 = moderate hyperplasia with tissue covering up to 1/2 of the crown 3 = marked hyperplasia with tissue on more than 1/2 the crown

This index was modified to include an assessment of the vertical component of GO (King & Fullinfaw, 1993) (Table 7) The vertical measurement was assessed on a three point scale; 0 = normal width of free gingival margin; 1 = thickening from normal up to 2 mm; 2 = thickening from normal greater than 2 mm. Alginate impressions were taken when possible. If alginate impressions were not possible, the GO was assessed chairside by the investigator.

Table 7 Horizontal Dimension Score Modification to the Hyperplastic Index
Vertical dimension score 0 = normal width of free gingival margin 1 = thickening from normal up to 2 mm 2 = thickening from the normal greater than 2 mm

It was apparent, after discussions with the medical staff, that in this study group alginate impressions at each appointment were impractical due to jaw dysfunction, undetermined periodontal status and patient stamina. The Gingival Overgrowth Index, a modification by Angelopoulos and Goaz, assesses the vertical dimension and the gingival changes in the development of GO. A score of "1" indicates mild GO with a thickening of the marginal gingiva and/or lobular granulation of the gingival pocket with enlargement covering up to one-third of the crown. GO

extending to the middle of the tooth scores "2" for moderate GO, and GO extending to two-thirds or more of the crown or affecting the attached gingiva is scored "3" for severe GO.

Table 8 Gingival Overgrowth or Enlargement by Angelopoulos & Goaz
0 = no GO 1 = mild GO (thickening of the marginal gingiva and/or lobular granulation of the gingival pocket with GO covering up to 1/3 of the crown) 2 = moderate GO (overgrowth extending to the middle of the crown) 3 = severe GO (overgrowth covering 2/3 of the crown or affectation of the attached gingiva)

CYA-induced GO is frequently described as raspberry-like in appearance with the inflammation represented by red glazed tissues. It is not fibrotic and pale as described in the phenytoin literature. The Angelopoulos & Goaz Index is an effective measurement for recording lobular tissue changes that occur in CYA GO. Papillae are often irregularly swollen or lobulated near the apex and may extend on to the crown without affecting the marginal tissue. GO was recorded at each appointment.

3.6 Quality of Life Visual Analogue Scale

Patients were asked to complete a Quality of Life (QOL) Visual Analogue Scale at the initial and final appointments. Transplant patients on CYA and other immuno-supressive agents report a higher QOL than a control group of a healthy population (Evans, 1991). Quality of life is a subjective assessment and is influenced by many factors. Self-assessment of QOL is relative to other life events (Locker et al., 2000). For example, after a life threatening situation, day-to-day stressors become less important and QOL may be assessed higher than the day before the life threatening event. Likewise, oral function may be taken for granted until oral complications

from new medications disrupt function and cause pain (Allison et al., 1997). However, self-assessment scales are an effective tool for patients to report pain levels and efficacy of drug treatments (Lubeck, 2002; Dickerson and Oakley, 1995). The QOL Visual Analogue Scale was included to assess any correlation between patient perception of QOL and the impact of changes in oral health.

3.7 Statistical Analysis

The Statistical Package for the Social Sciences, SPSS, was used to analyze the data. One-way analysis of variance (ANOVA) was used to analyze plaque scores versus bleeding, colour, tone, attachment loss and gingival enlargement. ANOVA reduces the risk of type one errors. Two sets of data were computed, one with the Silnes & Loe Plaque Index and the other with the O'Leary Plaque Index. Pearson correlation was used to correlate plaque indices to maximum opening and Quality of Life Visual Analogue scores as well as maximum opening and QOL scores. Cross-tabulations were constructed using Cohen's Kappa to analyze attachment loss versus tone, bleeding and colour.

3.8 Ethical Approval

Ethical approval was obtained from the Ethical Review Board for Research on Human Subjects at The University of British Columbia.

Chapter 4: Results

4.1 Study Population

The total number of participants who completed the study was 28: 22 were on cyclosporin and six took methotrexate. The subjects were predominately Caucasian (92%), with 4% Native and 4% Asian. Their ages ranged from 28 to 76 years of age with a mean age of 49.86 years (SD 9.69 yrs). The study population was 68% women and 32% men (Table 9). Cyclosporin dosages were comparable to current treatment dosages for transplant patients (Table 9). Dosages were based on the patient's weight to a maximum of 5 mg/kg/day. The mean daily dosage was 270.45 mg/day. Patient dosages were between 150-400 mg/day with a median dose of 250 mg/day.

Patient participation and co-operation was excellent. Of the people who applied to be volunteers for the CYA study, 97% agreed to be part of this study. Seven individuals were excluded from the study due to the discontinuation of the study medication. Reasons reported for withdrawal from the CYA trial related to side effects that were determined to be unacceptable. The side effects were predominately related to increasingly compromised liver function and secondarily for gastrointestinal upset. One patient was withdrawn due to death from cardiac arrest. Reasons for withdrawal unrelated to this study were not reported to the investigator in any detail.

Table 9	Patient Gender Profile	
	Cyclosporin	Methotrexate
Men	8 (36%)	1 (17%)
Women	14 (64%)	5 (83%)

4.2 Gingival Overgrowth

There was no gingival overgrowth in any of the patients. GO did not correlate to plaque scores or any other variable (see Appendix).

4.3 Gingival Inflammation

The CYA group had a mean plaque index of 0.94 (SD±50) using the Silness & Loe Plaque Index (Table 10). The MTX group had a mean plaque score of 0.86 (SD ± 0.82). The scores are comparable and indicate fair to good oral hygiene. Using the O'Leary Index, the CYA group had a mean plaque score of 55.66% (SD ± 25.77%). A score of 10% is considered good oral hygiene. There was no significant correlation between tone and the O'Leary Plaque index (Table 11). The MTX group had a mean score of 43.75 (SD ± 20.16), indicating less plaque present. Plaque scores did not significantly correlate with tone using ANOVA.

Table 10:	Silness & Loe Plaque Index and Tone in CYA Patients	
	Tone	SD
Decrease	1.38542	.4708
No change	0.8745	.5193
Increase	0.9539	.2731
F-stat	16.59	p<.0001.

Table 11:	O'Leary Plaque Index and Tone in CYA Patients	
	Tone	SD
Decrease	68.6036	31.5898
No change	52.510	24.2920
Increase	69.9696	20.970
F-stat	10.45	p<.0001

4.3.1 Bleeding and Colour

There was a decrease in mean bleeding scores for 20.8% of the CYA patients and an increase for 11.7% of them. In the MTX group, 7% had a decrease and 10.5% had an increase in mean bleeding scores (Table 12).

Table 12	CYA Group: Change in bleeding, tone, and colour		
	Bleeding	Tone	Colour
Decrease	20.8%	6.1%	14.1%
Increase	11.7%	5.0%	7.8%

14.1% of the CYA group demonstrated a decrease in colour score and 7.8% had an increase. The MTX group had less change with 1.4% having a decrease and 5.6% showing an increase in colour score (Table 13).

Table 13:	MTX Group: Change in bleeding, tone and colour		
	Bleeding	Tone	Colour
Decrease	7.0%	0	1.4%
Increase	10.5%	16.1	5.6%

One-way analysis of variance is used to analyze the relationship of plaque versus bleeding and colour. The findings for plaque and bleeding, plaque and tone and plaque and colour using the Silness & Loe Plaque Index were not statistically significant. Plaque and colour were weakly significant using the O'Leary Index.

There was a weak inverse relationship between plaque and colour, with higher plaque scores having a reduced colour score.

TABLE 14

Silness and Loe				
	Bleeding	SD	Colour	SD
Decrease	1.0684	1.0684	1.2428 1	0.5549
No change	0.8410	.8410	0.8437	0.4389
Increase	1.0217	1.0217	0.9658	0.3468
F-stat	10.74		21.88	
	P<.0001		p<.0001	
O'Leary Plaque Index				
	Bleeding	SD	Colour	SD
Decrease	58.0792	27.5437	61.9538	30.9049
No change	51.7765	23.7314	52.4703	23.9072
Increase	62.6148	26.3918	59.5278	22.8954
F-stat	5.72		4.82	
	p=.0035		p=.0085	

4.4 Quality of Life

Quality of life was found to correlate to maximum opening. The mean quality of life at the beginning of the study was 70.09 (SD±17.38) for the CYA group and 67.67 (SD ± 25.97) for the MTX group. At the completion of the study QOL was 66.5 (SD ±21.42) for the CYA group and 60.67 (SD ± 26.67) for the MTX group. The mean difference was -3.59 for the CYA group and -7.00 for the MTX group.

Participants who had improved joint function self-rated a higher quality of life on the visual analogue scale. Patients with reduced maximum opening reported lower quality of life scores (Table 15). Patients were not asked to relate maximum opening to quality of life and nor were they asked to specifically relate oral health to their quality of life when completing the visual analogue scale. At the completion of the

last exam patients were asked to complete an Oral Health Impact Profile questionnaire the results of which are not part of this study.

Table 15: Quality of Life Scores

CYA	MEAN	SD	MIN	MAX
QOL start	70.09	17.38	33	98
QOL end	66.5	21.42	29	100
Difference	-3.59	21.90	-59	+36
MTX	MEAN	SD	MIN	MAX
QOL start	67.67	25.97	34	97
QOL end	60.67	26.67	35	92
Difference	-7.0	15.32	-37	6

Pearson correlations were used to compute the relationship between quality of life and maximum opening. There was an inverse relationship between initial QOL and maximum opening (Figure 2).

Figure 2 CYA Initial QOL vs Max Opening

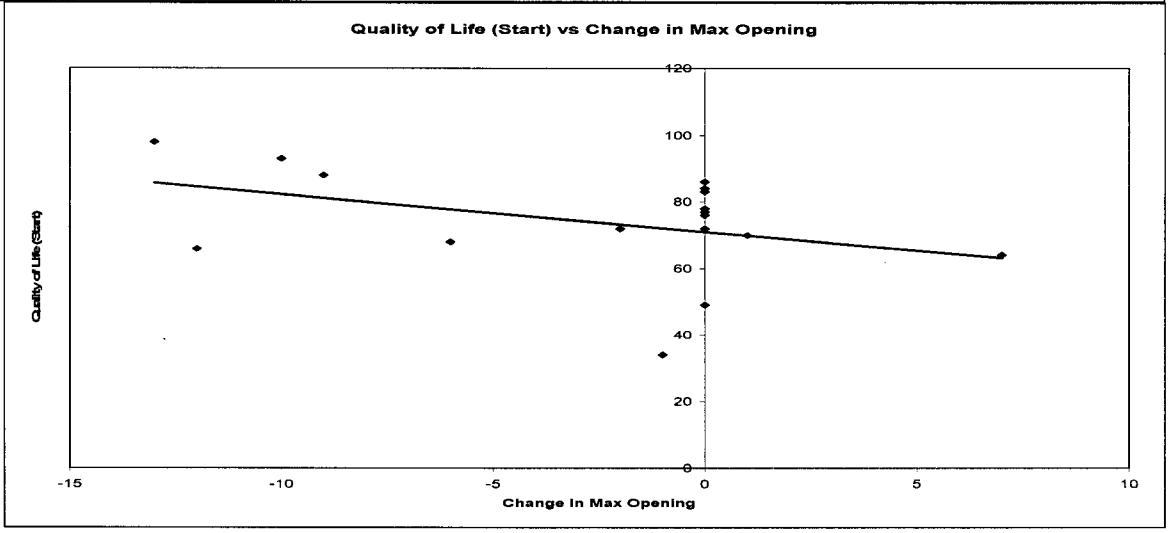
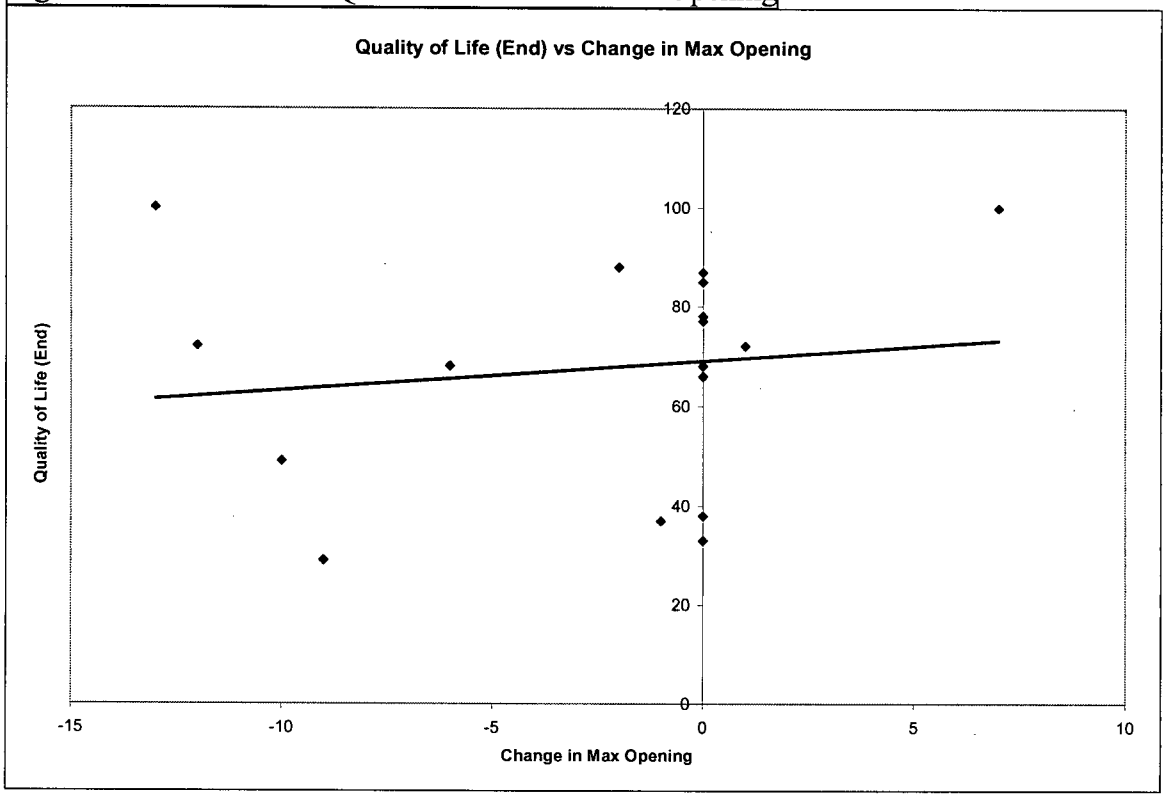
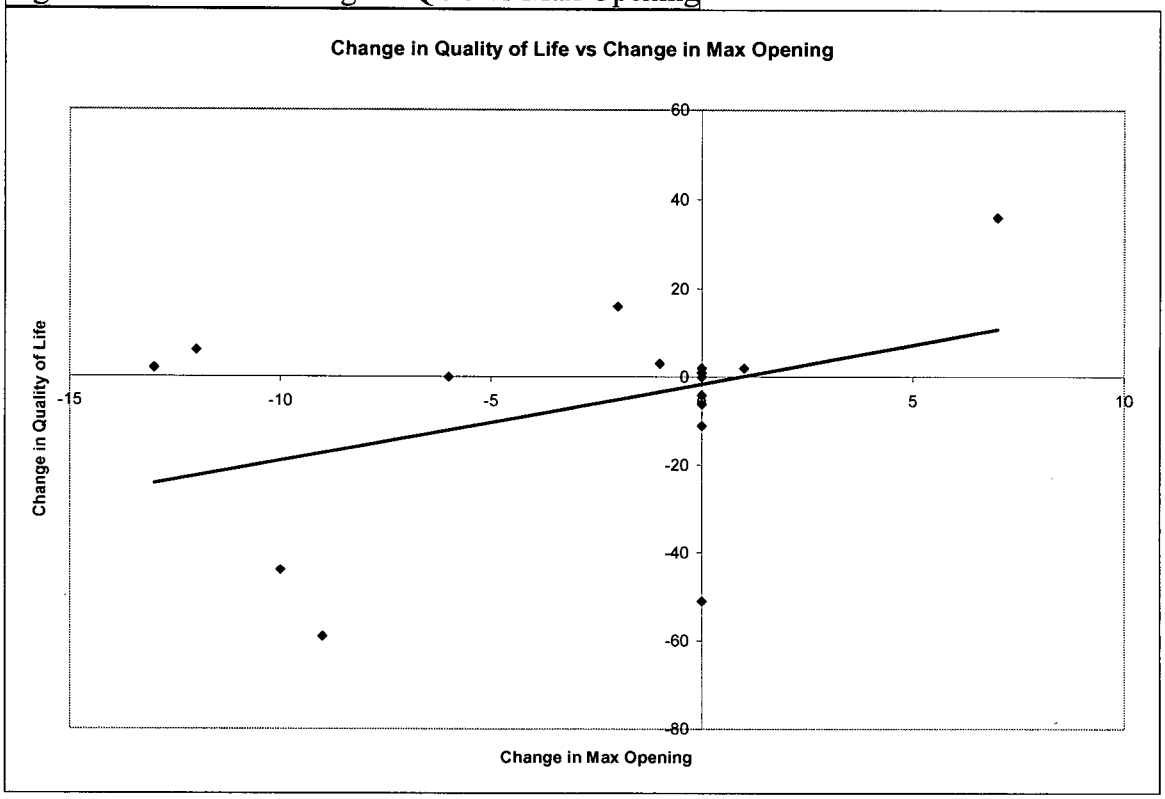


Figure 3 CYA End QOL Score vs Maximum Opening



Individuals who had an increase in joint function reported an increased QOL at the completion of the study (Figure 3).

Figure 4 CYA Change in QOL vs Max Opening



Changes in QOL correlated with maximum opening. Patients with a negative change in maximum opening at the completion of the study reported a lower QOL than at the start of the study (Figure 4).

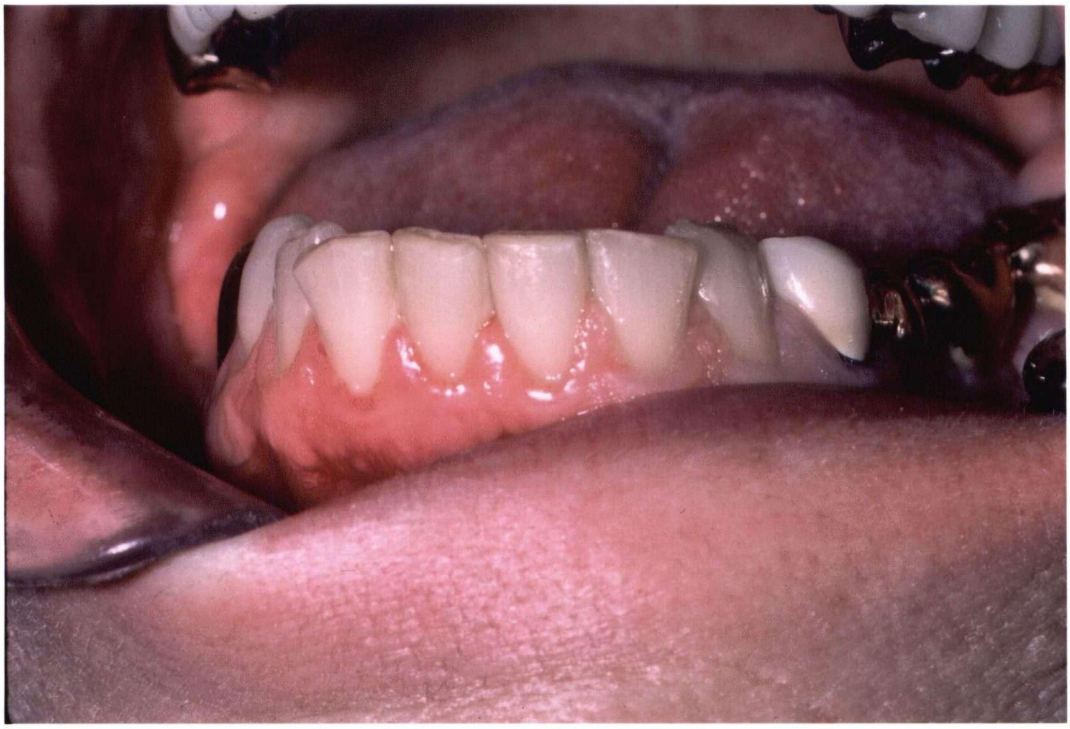
CHAPTER 5: DISCUSSION

5.1 Gingival Overgrowth

The role of CYA on the incidence of GO is not consistent between studies. None of the participants in this study demonstrated any manifestations of CYA-induced GO. The frequency of CYA-induced GO has been reported as high as 70% in Type I diabetes patients. The weak correlation between plaque and GO may be related to the increased challenge of removing plaque from the irregularities created by GO. Medication dosage also did not relate to the incidence of GO in the diabetic group. Many studies have shown that dose is unrelated (Daly, 1992; Daley et al., 1986; Wysocki et al., 1983; M^{c}Gaw et al., 1987; Seymour, 1991). Renal transplant patient studies have reported a 48% incidence of GO. The indices used may reflect a false positive. A Silness & Loe Plaque Index score of "2", which indicates significant plaque levels, scored only "1" on the hyperplastic index defined as blunting of the interdental papilla. These findings show that individuals with moderate plaque demonstrate the early signs of inflammation but it is reported as GO (Figure 5). A plaque score of "2" would be expected in a healthy population, or a non-CYA treatment group—some inflammatory response with blunting and bleeding, the usual early manifestations of gingivitis (Van der Weijden et al., 1994; Wilkins, 1999). Studies reporting significant incidence of GO state that the average scores of patients with GO were "1.2" on the hyperplastic index, indicating relatively low severities of tissue changes. This may also be attributed to signs of gingival inflammation (Haffajee et al., 1991). Other studies combined scores of "1" and "0" due to

examiner inability to calibrate on these two scores (Hefti et al., 1994). The incidence of GO was significantly reduced from earlier studies.

Figure 5: CYA Patient's Gingival Condition Day Zero: blunting and lobular changes evident prior to initiation of drug therapy



The majority of CYA-induced studies are cross sectional (Savage et al., 1987; Montebugnoli et al., 1996; King & Fullinfaw, 1993). Longitudinal studies are usually initiated after drug therapy and the presence of GO is evident. Existing gingival inflammation would be recorded as mild GO and would inflate the prevalence of GO.

Type I diabetics are more at risk for GO as children and adolescents than as adults. Adult renal transplant patients have a greater frequency of GO than children in the same population group. Studies reporting age as a significant factor state that the first and second decades are the years most likely to have GO. In heart transplant patients, the highest incidence of GO was in the second and third decades of life (Somacarrera et al., 1994a). This study group did not have any participants in the child or adolescent years. The youngest patient in the RA study group was in her third decade and the eldest in her eighth decade. There were no significant findings associated with aging in this study. A larger study population with children and adolescents is required to determine if RA patients respond similarly to Type I diabetes patients.

The dosages of CYA in this study are comparable to renal transplant dosages. The literature indicates that dosage is not a causative factor, therefore the lack of GO can not be attributed to low dose CYA (Wysocki et al., 1983; McGaw et al., 1987; Seymour, 1991).

It is possible that different existing immunological conditions affect the influence of CYA on gingival tissues. In heart transplant patients, CYA-induced GO decreased or resolved over time without intervention. Patients in this study had improvements in

GI evidenced by reductions in redness. Heart transplant patients taking CYA for less than 36 months showed more GO than patients on CYA for longer than 36 months, demonstrating that GO is not simply a pharmacokinetic phenomenon (Montebugnoli et al., 1996). The unique immune system of RA patients may response differently to CYA than other populations. Systemic Lupus Erythematosus, a rhematoid disease, affects kidney function. SLS sufferers develop renal dysfunction as a manifestation of their primary disease. When renal transplants were undertaken, the long-term survival rate for SLS renal transplants was significant higher than for non-SLS patients (Roth et al., 1987). Further study of the effects of CYA in RA populations is required.

Figure 6: Tissue Changes in a Patient on Cyclosporin Day Zero; edema, lobular changes and redness are evident prior to drug therapy

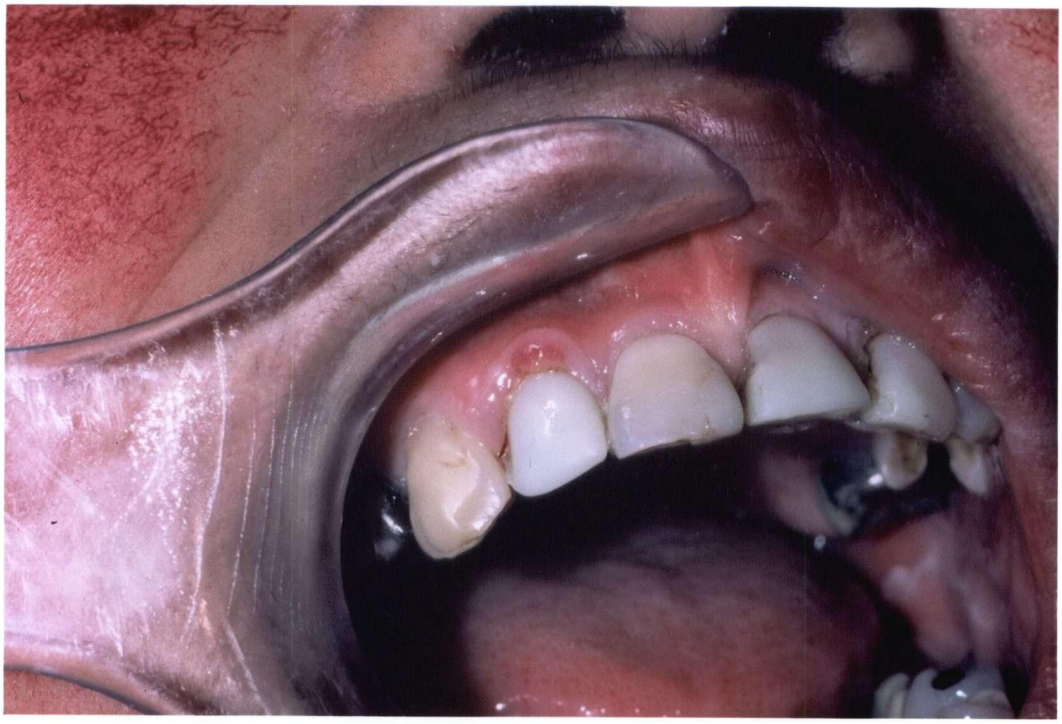


Figure 7: Tissue Changes in a Patient on Cyclosporin Day Sixty; a reduction in redness is evident

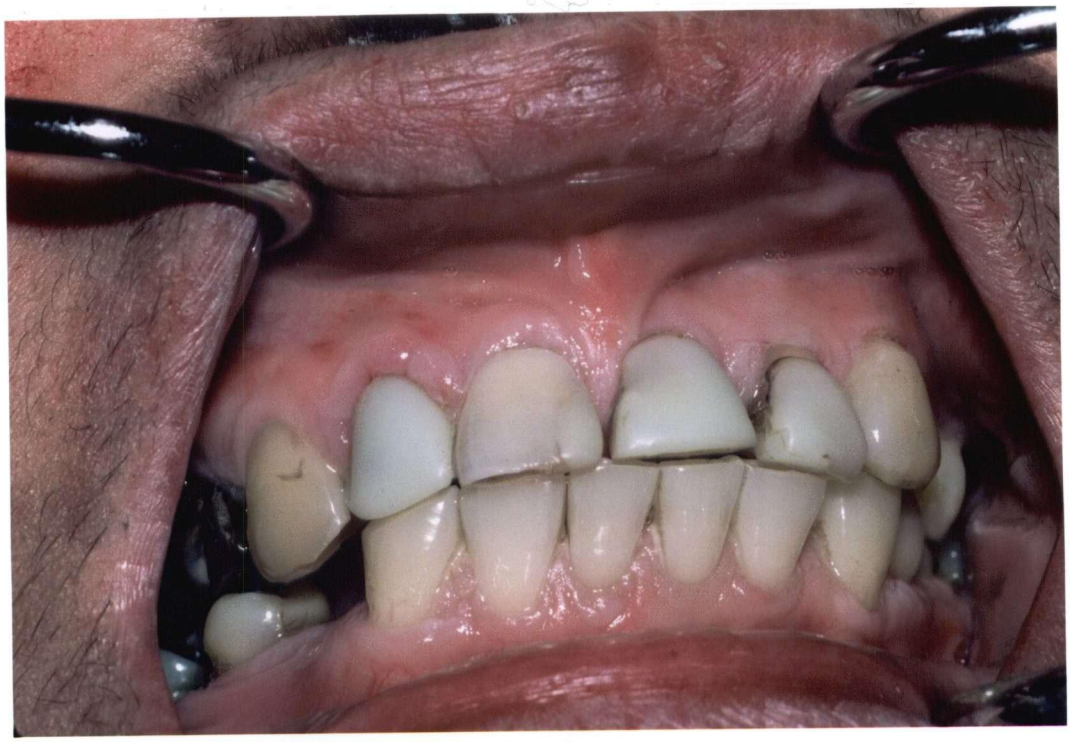
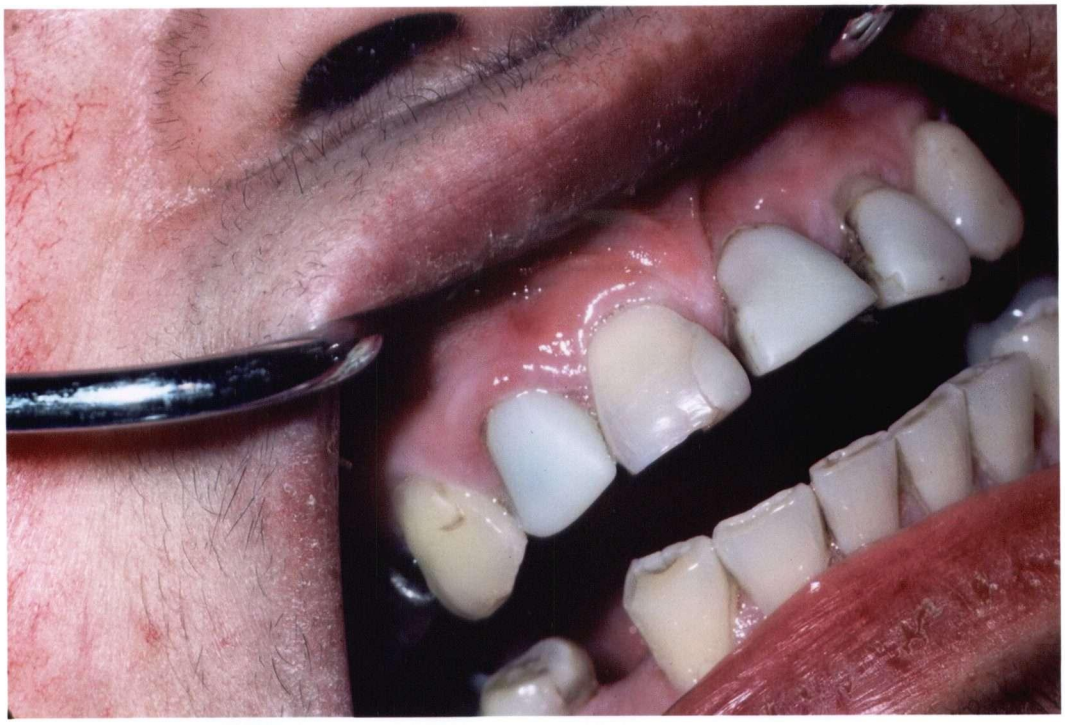


Figure 8: Tissue Changes in a Patient on Cyclosporin Day Ninety; decreased redness and edema/lobulation are evident



5.2 Gingival Inflammation and Bleeding

There were no significant findings for the relationship of GI and GO in this study. Bleeding and tone did not significantly relate to plaque scores. The absence of GO negates any relationship between GI and GO. There was a weak inverse relationship between colour and plaque using the O'Leary Plaque Index. A slight decrease in colour occurred in patients with marked inflammation scores. This was an unanticipated result. Previous CYA studies that report a decrease in GO may have been observing a decrease in GI that was not recorded in initial observations.

5.3 Quality of Life

Quality of life is a subjective measure and significantly influenced by life events (Evans, 1991). Study participants may have been optimistic about the potential of a new drug regime for the management of their disease. Participants in the drug trial had severe or aggressive RA and were considered non-responsive to routine treatment regimes including MTX. Patients who did not perceive a benefit of increased function and reduced pain may have viewed their quality of life as poorer than those who felt their disease was being controlled by the new medication (Allison et al., 1997).

5.4 Future Considerations

More longitudinal studies are required to examine pre-existing conditions more effectively prior to the initiation of CYA therapy. The oral condition of individuals with RA needs to be researched and isolated from other rheumatoid conditions. Change in tissue, and not present condition, needs to be reported more frequently to ensure accurate reporting of GO and not GI. This will narrow the evidence

surrounding the incidence of GO and may clarify causative factors. GI is considered to be an immunological response and consideration must be given to the effect of a suppressed immune system on existing GI. The role of CYA on the immune response during a phase of periodontal breakdown may lead to the development of alternative periodontal treatments using immunosuppressive drugs (Kjeldsen et al., 1993).Topical treatments may be able to affect inflammatory immune responses without the undesirable systemic toxicity.

CHAPTER 6: CONCLUSION

The effect of cyclosporin on human gingival tissues was not evident in this study. Instead of the anticipated appearance of gingival overgrowth, there was a reduction of the existing inflammation in the participants' gingivae. Traditional theories of gingival inflammation and periodontal diseases are linked with the host response to pathogens. For disease to occur, there must be a virulent pathogen in sufficient numbers, the host must be susceptible, and the environment must be conducive to the pathogen (Socransky et al., 1992; Socransky & Haffajee, 1991). During this study, one of these areas may have been affected to result in a decrease in inflammation. Plaque levels remained constant. Oral hygiene instruction was not given and patients continued with previously-established care routines. Cyclosporin may impact the virulence of mouth bacteria or its ability to produce endotoxins to stimulate an inflammatory response in the host. Pathogens may adapt to the environment, altering their own virulence factors, if CYA creates an inhospitable environment. CYA affects the activity of T cells and the production of IL-1, which plays a role in the process of periodontal disease and tissue inflammation. IL-1 is increased in the gingival fluids extracted from inflamed sites in periodontal patients. Mouse splenic lymphocytes are more sensitive to CYA than LPS, which may reduce the host inflammatory response to putative pathogens (Wiesinger & Borel, 1979). The synthesis of IL-1 is inhibited by CYA, yet studies report histological changes in fibroblasts. Fibroblasts in CYA lesions have increased cytoplasmic volume but not number. With IL-1 inhibited, another mechanism in some individuals may impact

fibroblast development, resulting in GO responders and non-responders in CYA patient populations. The host's ability to regulate fibroblast integrity may be compromised by the presence of CYA. The impact of IL-1 on collagen or collagenase may impact gingival overgrowth formation. Fibroblasts may be aging abnormally due to poor growth regulation.

Patients demonstrating GO may be having an abnormal inflammatory response. With cellular immunity reduced, alternative mechanisms may be responding to specific mitogens. Healing mechanisms may be altered. The regulation of tissue remodeling may be compromised if IL-1 and fibroblast function is compromised. The prevalence of GO may have been overstated in early studies. Early studies may not have recognized calcium channel blockers as GO-inducing medications. A common side effect of CYA is hypertension, so the influence of calcium channel blockers on the reported frequency of GO may be significant. Nifedipine causes GO in 24%-38% of patients and 4% of the population demonstrates idiopathic GO (Steele & Schreiber, 1994). These factors are not accounted for in CYA studies. RA patients have a unique immune system and the effects of cyclosporin on gingival tissues requires further study.

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APPENDIX ONE

Gingival Overgrowth and Cyclosporin Study
-- statistical analysis and raw data

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Part I. Frequency Tables (per tooth), split by Group

A. CYA

MBLEED Mesial - Bleeding

Value Label	Value	Frequency	Percent	Valid Percent
	-2	14	2.7	3.0
	-1	42	8.0	9.1
	0	372	70.5	80.7
	1	20	3.8	4.3
	2	12	2.3	2.6
	3	1	.2	.2
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

FBLEED Facial - Bleeding

Value Label	Value	Frequency	Percent	Valid Percent
	-2	9	1.7	2.0
	-1	7	1.3	1.5
	0	430	81.4	93.3
	1	10	1.9	2.2
	2	5	.9	1.1
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

DBLEED Distal - Bleeding

Value Label	Value	Frequency	Percent	Valid Percent
	-2	20	3.8	4.3
	-1	45	8.5	9.8
	0	370	70.1	80.3
	1	16	3.0	3.5
	2	10	1.9	2.2
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

MTONE Mesial - Tone

Value Label	Value	Frequency	Percent	Valid Percent
	-2	10	1.9	2.2
	-1	7	1.3	1.5
	0	430	81.4	93.3
	1	14	2.7	3.0
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

FTONE Facial - Tone

Value Label	Value	Frequency	Percent	Valid Percent
	-2	2	.4	.4
	-1	4	.8	.9
	0	451	85.4	97.8
	1	4	.8	.9
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

DTONE Distal - Tone

Value Label	Value	Frequency	Percent	Valid Percent
	-2	12	2.3	2.6
	-1	7	1.3	1.5
	0	429	81.3	93.1
	1	13	2.5	2.8
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

MCOLOUR Mesial - Colour

Value Label	Value	Frequency	Percent	Valid Percent
	-2	12	2.3	2.6
	-1	40	7.6	8.7
	0	399	75.6	86.6
	1	10	1.9	2.2
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

FCOLOUR Facial - Colour

Value Label	Value	Frequency	Percent	Valid Percent
	-2	13	2.5	2.8
	-1	14	2.7	3.0
	0	409	77.5	88.7
	1	25	4.7	5.4
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

DCOLOUR Distal - Colour

Value Label	Value	Frequency	Percent	Valid Percent
	-2	12	2.3	2.6
	-1	38	7.2	8.2
	0	402	76.1	87.2
	1	9	1.7	2.0
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

MATTACH Mesial - Attachment

Value Label	Value	Frequency	Percent	Valid Percent
	-4	1	.2	.2
	-3	2	.4	.4
	-2	7	1.3	1.5
	-1	56	10.6	12.1
	0	327	61.9	70.9
	1	59	11.2	12.8
	2	9	1.7	2.0
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

FATTACH Facial - Attachment

Value Label	Value	Frequency	Percent	Valid Percent
	-2	5	.9	1.1
	-1	29	5.5	6.3
	0	366	69.3	79.4
	1	59	11.2	12.8
	2	2	.4	.4
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

DATTACH Distal - Attachment

Value Label	Value	Frequency	Percent	Valid Percent
	-3	1	.2	.2
	-2	3	.6	.7
	-1	38	7.2	8.2
	0	353	66.9	76.6
	1	57	10.8	12.4
	2	8	1.5	1.7
	4	1	.2	.2
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

TBLEED Total - Bleeding

Value Label	Value	Frequency	Percent	Valid Percent
	-6	5	.9	1.1
	-4	4	.8	.9
	-3	3	.6	.7
	-2	30	5.7	6.5
	-1	54	10.2	11.7
	0	311	58.9	67.5
	1	24	4.5	5.2
	2	25	4.7	5.4
	3	3	.6	.7
	4	1	.2	.2
	5	1	.2	.2
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

TTONE Total - Tone

Value Label	Value	Frequency	Percent	Valid Percent
	-6	1	.2	.2
	-4	9	1.7	2.0
	-2	4	.8	.9
	-1	14	2.7	3.0
	0	410	77.7	88.9
	1	19	3.6	4.1
	2	2	.4	.4
	3	2	.4	.4
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

TCOLOUR Total - Colour

Value Label	Value	Frequency	Percent	Valid Percent
	-6	12	2.3	2.6
	-3	11	2.1	2.4
	-2	16	3.0	3.5
	-1	26	4.9	5.6
	0	360	68.2	78.1
	1	31	5.9	6.7
	2	5	.9	1.1
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

TATTACH Total - Attachment

Value Label	Value	Frequency	Percent	Valid Percent
	-6	1	.2	.2
	-4	3	.6	.7
	-3	6	1.1	1.3
	-2	24	4.5	5.2
	-1	58	11.0	12.6
	0	250	47.3	54.2
	1	66	12.5	14.3
	2	37	7.0	8.0
	3	11	2.1	2.4
	4	5	.9	1.1
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

MBLEED2 Mesial-Bleeding (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
Decrease	-1	56	10.6	12.1
No Change	0	372	70.5	80.7
Increase	1	33	6.3	7.2
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

FBLEED2 Facial-Bleeding (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
Decrease	-1	16	3.0	3.5
No Change	0	430	81.4	93.3
Increase	1	15	2.8	3.3
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

DBLEED2 Distal-Bleeding (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
Decrease	-1	65	12.3	14.1
No Change	0	370	70.1	80.3
Increase	1	26	4.9	5.6
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

MTONE2 Mesial-Tone (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
Decrease	-1	17	3.2	3.7
No Change	0	430	81.4	93.3
Increase	1	14	2.7	3.0
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

FTONE2 Facial-Tone (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
Decrease	-1	6	1.1	1.3
No Change	0	451	85.4	97.8
Increase	1	4	.8	.9
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

DTONE2 Distal-Tone (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
Decrease	-1	19	3.6	4.1
No Change	0	429	81.3	93.1
Increase	1	13	2.5	2.8
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

MCOLOUR2 Mesial-Colour (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
Decrease	-1	52	9.8	11.3
No Change	0	399	75.6	86.6
Increase	1	10	1.9	2.2
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

FCOLOUR2 Facial-Colour (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
Decrease	-1	27	5.1	5.9
No Change	0	409	77.5	88.7
Increase	1	25	4.7	5.4
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

DCOLOUR2 Distal-Colour (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
Decrease	-1	50	9.5	10.8
No Change	0	402	76.1	87.2
Increase	1	9	1.7	2.0
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

MATTACH2 Mesial-Attachment (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
Decrease	-1	66	12.5	14.3
No Change	0	327	61.9	70.9
Increase	1	68	12.9	14.8
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

FATTACH2 Facial-Attachment (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
Decrease	-1	34	6.4	7.4
No Change	0	366	69.3	79.4
Increase	1	61	11.6	13.2
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

DATTACH2 Distal-Attachment (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
Decrease	-1	42	8.0	9.1
No Change	0	353	66.9	76.6
Increase	1	66	12.5	14.3
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

TBLEED2 Total-Bleeding (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
Decrease	-1	96	18.2	20.8
No Change	0	311	58.9	67.5
Increase	1	54	10.2	11.7
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

TTONE2 Total-Tone (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
Decrease	-1	28	5.3	6.1
No Change	0	410	77.7	88.9
Increase	1	23	4.4	5.0
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

TCOLOUR2 Total-Colour (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
Decrease	-1	65	12.3	14.1
No Change	0	360	68.2	78.1
Increase	1	36	6.8	7.8
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

TATTACH2 Total-Attachment (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
Decrease	-1	92	17.4	20.0
No Change	0	250	47.3	54.2
Increase	1	119	22.5	25.8
	.	67	12.7	Missing
	Total	528	100.0	100.0

Valid cases 461 Missing cases 67

B. MTX

MBLEED Mesial - Bleeding

Value Label	Value	Frequency	Percent	Valid Percent
	-1	7	4.9	4.9
	0	127	88.2	88.8
	1	8	5.6	5.6
	2	1	.7	.7
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

FBLEED Facial - Bleeding

Value Label	Value	Frequency	Percent	Valid Percent
	-1	1	.7	.7
	0	140	97.2	97.9
	2	2	1.4	1.4
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

DBLEED Distal - Bleeding

Value Label	Value	Frequency	Percent	Valid Percent
	-1	6	4.2	4.2
	0	127	88.2	88.8
	1	9	6.3	6.3
	2	1	.7	.7
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

MTONE Mesial - Tone

Value Label	Value	Frequency	Percent	Valid Percent
	0	139	96.5	97.2
	1	3	2.1	2.1
	2	1	.7	.7
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

FTONE Facial - Tone

Value Label	Value	Frequency	Percent	Valid Percent
	0	124	86.1	86.7
	1	18	12.5	12.6
	2	1	.7	.7
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

DTONE Distal - Tone

Value Label	Value	Frequency	Percent	Valid Percent
	0	141	97.9	98.6
	1	1	.7	.7
	2	1	.7	.7
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

MCOLOUR Mesial - Colour

Value Label	Value	Frequency	Percent	Valid Percent
	0	139	96.5	97.2
	1	4	2.8	2.8
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

FCOLOUR Facial - Colour

Value Label	Value	Frequency	Percent	Valid Percent
	-1	2	1.4	1.4
	0	138	95.8	96.5
	1	2	1.4	1.4
	2	1	.7	.7
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

DCOLOUR Distal - Colour

Value Label	Value	Frequency	Percent	Valid Percent
	0	140	97.2	97.9
	1	3	2.1	2.1
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

MATTACH Mesial - Attachment

Value Label	Value	Frequency	Percent	Valid Percent
	-1	10	6.9	7.0
	0	123	85.4	86.0
	1	9	6.3	6.3
	4	1	.7	.7
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

FATTACH Facial - Attachment

Value Label	Value	Frequency	Percent	Valid Percent
	-1	17	11.8	11.9
	0	118	81.9	82.5
	1	8	5.6	5.6
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

DATTACH Distal - Attachment

Value Label	Value	Frequency	Percent	Valid Percent
	-1	9	6.3	6.3
	0	124	86.1	86.7
	1	8	5.6	5.6
	2	1	.7	.7
	4	1	.7	.7
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

TBLEED Total - Bleeding

Value Label	Value	Frequency	Percent	Valid Percent
	-2	1	.7	.7
	-1	9	6.3	6.3
	0	118	81.9	82.5
	1	12	8.3	8.4
	2	1	.7	.7
	4	2	1.4	1.4
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

TTONE Total - Tone

Value Label	Value	Frequency	Percent	Valid Percent
	0	120	83.3	83.9
	1	22	15.3	15.4
	6	1	.7	.7
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

TCOLOUR Total - Colour

Value Label	Value	Frequency	Percent	Valid Percent
	-1	2	1.4	1.4
	0	133	92.4	93.0
	1	7	4.9	4.9
	4	1	.7	.7
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

TATTACH Total - Attachment

Value Label	Value	Frequency	Percent	Valid Percent
	-3	1	.7	.7
	-2	4	2.8	2.8
	-1	19	13.2	13.3
	0	95	66.0	66.4
	1	21	14.6	14.7
	2	1	.7	.7
	3	2	1.4	1.4
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

MBLEED2 Mesial-Bleeding (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
Decrease	-1	7	4.9	4.9
No Change	0	127	88.2	88.8
Increase	1	9	6.3	6.3
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

FBLEED2 Facial-Bleeding (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
Decrease	-1	1	.7	.7
No Change	0	140	97.2	97.9
Increase	1	2	1.4	1.4
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

DBLEED2 Distal-Bleeding (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
Decrease	-1	6	4.2	4.2
No Change	0	127	88.2	88.8
Increase	1	10	6.9	7.0
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

MTONE2 Mesial-Tone (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
No Change	0	139	96.5	97.2
Increase	1	4	2.8	2.8
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

FTONE2 Facial-Tone (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
No Change	0	124	86.1	86.7
Increase	1	19	13.2	13.3
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

DTONE2 Distal-Tone (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
No Change	0	141	97.9	98.6
Increase	1	2	1.4	1.4
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

MCOLOUR2 Mesial-Colour (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
No Change	0	139	96.5	97.2
Increase	1	4	2.8	2.8
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

FCOLOUR2 Facial-Colour (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
Decrease	-1	2	1.4	1.4
No Change	0	138	95.8	96.5
Increase	1	3	2.1	2.1
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

DCOLOUR2 Distal-Colour (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
No Change	0	140	97.2	97.9
Increase	1	3	2.1	2.1
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

MATTACH2 Mesial-Attachment (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
Decrease	-1	10	6.9	7.0
No Change	0	123	85.4	86.0
Increase	1	10	6.9	7.0
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

FATTACH2 Facial-Attachment (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
Decrease	-1	17	11.8	11.9
No Change	0	118	81.9	82.5
Increase	1	8	5.6	5.6
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

DATTACH2 Distal-Attachment (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
Decrease	-1	9	6.3	6.3
No Change	0	124	86.1	86.7
Increase	1	10	6.9	7.0
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

TBLEED2 Total-Bleeding (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
Decrease	-1	10	6.9	7.0
No Change	0	118	81.9	82.5
Increase	1	15	10.4	10.5
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

TTONE2 Total-Tone (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
No Change	0	120	83.3	83.9
Increase	1	23	16.0	16.1
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

TCOLOUR2 Total-Colour (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
Decrease	-1	2	1.4	1.4
No Change	0	133	92.4	93.0
Increase	1	8	5.6	5.6
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

TATTACH2 Total-Attachment (categoric)

Value Label	Value	Frequency	Percent	Valid Percent
Decrease	-1	24	16.7	16.8
No Change	0	95	66.0	66.4
Increase	1	24	16.7	16.8
	.	1	.7	Missing
	Total	144	100.0	100.0

Valid cases 143 Missing cases 1

Part II. Descriptive Statistics (per patient)

GRP Group: MTX or CYA

Value Label	Value	Frequency	Percent	Valid Percent
MTX	1	6	21.4	21.4
CYA	2	22	78.6	78.6
	Total	28	100.0	100.0

A. CYA

Variable	Description	Mean	SD	Min	Max	N
SILNESS	Silness & Loe Plaque Index	.94	.50	0	2	22
OLEARY	Oleary Plaque Index (%)	55.66	25.77	11	100	22
MAXOPEN1	Max Opening-start	41.41	10.90	21	66	17
MAXOPEN2	Max Opening-end	36.35	7.88	22	48	17
MAXOPEND	Max Opening-difference	-2.65	5.40	-13	7	17
QOL1	Quality of Life - start	70.09	17.38	33	98	22
QOL2	Quality of Life - end	66.50	21.42	29	100	22
QOLD	Quality of Life - difference	-3.59	21.90	-59	36	22

B. MTX

Variable	Description	Mean	SD	Min	Max	N
SILNESS	Silness & Loe Plaque Index	.86	.82	0	2	6
OLEARY	Oleary Plaque Index (%)	43.72	20.16	18	75	6
MAXOPEN1	Max Opening-start	34.50	7.58	21	42	6
MAXOPEN2	Max Opening-end	34.17	7.00	24	42	6
MAXOPEND	Max Opening-difference	-.33	2.58	-5	3	6
QOL1	Quality of Life - start	67.67	25.97	34	97	6
QOL2	Quality of Life - end	60.67	26.67	35	92	6
QOLD	Quality of Life - difference	-7.00	15.32	-37	6	6

Part III. Comparisons between Variables - CYA Group Only

A. Plaque scores vs. max opening, quality of life

"Per patient" basis,
Pearson correlations are computed.

	MAXOPEN1	MAXOPEN2	MAXOPEND	QOL1	QOL2	QOLD
SILNESS	-.006	-.045	-.246	.189	-.050	-.199
OLEARY	.329	.127	-.152	-.054	-.158	-.112

None of these correlation coefficients are statistically significantly different from zero.

B. Quality of Life vs. max opening

"Per patient" basis, Pearson correlations are computed.

	QOL1	QOL2	QOLD
MAXOPEN1	-.134	-.535**	-.421*
MAXOPEN2	.379	-.210	-.447*
MAXOPEND	-.388	.139	.386

Note: * indicates a P-value < .10; ** indicates a P-value < .05

C. Plaque scores vs. bleeding, tone, colour, attachment loss

Note: Plaque scores are recorded on a "per patient" basis, while bleeding, tone, colour and attachment loss are recorded on a "per tooth" basis. One-way analysis of variance is used here. There are two sets of results, one for Silness & Loe and one for Oleary.

Summaries of SILNESS Silness & Loe Plaque Index
By levels of MBLEED2 Mesial-Bleeding (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			.9095	.4708	461
MBLEED2	-1	Decrease	1.1718	.6458	56
MBLEED2	0	No Change	.8585	.4211	372
MBLEED2	1	Increase	1.0388	.4956	33

F-stat = 12.73 ; P = .0001

Summaries of SILNESS Silness & Loe Plaque Index
By levels of FBLEED2 Facial-Bleeding (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			.9095	.4708	461
FBLEED2	-1	Decrease	1.3156	.6510	16
FBLEED2	0	No Change	.8886	.4582	430
FBLEED2	1	Increase	1.0747	.4042	15

F-stat = 7.51 ; P = .0006

Summaries of SILNESS Silness & Loe Plaque Index
By levels of DBLEED2 Distal-Bleeding (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			.9095	.4708	461
DBLEED2	-1	Decrease	1.1840	.5968	65
DBLEED2	0	No Change	.8509	.4234	370
DBLEED2	1	Increase	1.0577	.5006	26

F-stat = 16.21 ; P < .0001

Summaries of SILNESS Silness & Loe Plaque Index
By levels of MTONE2 Mesial-Tone (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			.9095	.4708	461
MTONE2	-1	Decrease	1.5265	.5272	17
MTONE2	0	No Change	.8822	.4574	430
MTONE2	1	Increase	1.0000	.2562	14

F-stat = 16.64 ; P < .0001

Summaries of SILNESS Silness & Loe Plaque Index
By levels of FTONE2 Facial-Tone (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			.9095	.4708	461
FTONE2	-1	Decrease	1.3883	.4565	6
FTONE2	0	No Change	.9034	.4691	451
FTONE2	1	Increase	.8775	.4018	4

F-stat = 3.18 ; P =.043

Summaries of SILNESS Silness & Loe Plaque Index
By levels of DTONE2 Distal-Tone (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			.9095	.4708	461
DTONE2	-1	Decrease	1.5221	.5349	19
DTONE2	0	No Change	.8799	.4551	429
DTONE2	1	Increase	.9900	.2139	13

F-stat = 18.42 ; P <.0001

Summaries of SILNESS Silness & Loe Plaque Index
By levels of MCOLOUR2 Mesial-Colour (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			.9095	.4708	461
MCOLOUR2	-1	Decrease	1.3083	.5770	52
MCOLOUR2	0	No Change	.8551	.4322	399
MCOLOUR2	1	Increase	1.0050	.3473	10

F-stat = 23.64 ; P <.0001

Summaries of SILNESS Silness & Loe Plaque Index
By levels of FCOLOUR2 Facial-Colour (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			.9095	.4708	461
FCOLOUR2	-1	Decrease	1.7900	.4000	27
FCOLOUR2	0	No Change	.8456	.4240	409
FCOLOUR2	1	Increase	1.0036	.2604	25

F-stat = 66.05 ; P <.0001

Summaries of SILNESS Silness & Loe Plaque Index
By levels of DCOLOUR2 Distal-Colour (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			.9095	.4708	461
DCOLOUR2	-1	Decrease	1.3200	.5801	50
DCOLOUR2	0	No Change	.8578	.4300	402
DCOLOUR2	1	Increase	.9389	.4753	9

F-stat = 23.55 ; P <.0001

Summaries of SILNESS Silness & Loe Plaque Index
By levels of MATTACH2 Mesial-Attachment (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			.9095	.4708	461
MATTACH2	-1	Decrease	1.0677	.4502	66
MATTACH2	0	No Change	.8874	.4764	327
MATTACH2	1	Increase	.8621	.4373	68

F-stat = 4.50 ; P =.012

Summaries of SILNESS Silness & Loe Plaque Index
By levels of FATTACH2 Facial-Attachment (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			.9095	.4708	461
FATTACH2	-1	Decrease	1.2312	.5321	34
FATTACH2	0	No Change	.8887	.4517	366
FATTACH2	1	Increase	.8548	.4876	61

F-stat = 9.01 ; P =.0001

Summaries of SILNESS Silness & Loe Plaque Index
By levels of DATTACH2 Distal-Attachment (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			.9095	.4708	461
DATTACH2	-1	Decrease	1.0257	.4310	42
DATTACH2	0	No Change	.8975	.4860	353
DATTACH2	1	Increase	.8998	.4030	66

F-stat = 1.41 ; P =.24

Summaries of SILNESS Silness & Loe Plaque Index
By levels of TBLEED2 Total-Bleeding (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			.9095	.4708	461
TBLEED2	-1	Decrease	1.0684	.5879	96
TBLEED2	0	No Change	.8410	.4046	311
TBLEED2	1	Increase	1.0217	.5105	54

F-stat = 10.74 ; P < .0001

Summaries of SILNESS Silness & Loe Plaque Index
By levels of TTONE2 Total-Tone (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			.9095	.4708	461
TTONE2	-1	Decrease	1.3854	.5193	28
TTONE2	0	No Change	.8745	.4589	410
TTONE2	1	Increase	.9539	.2731	23

F-stat = 16.59 ; P < .0001

Summaries of SILNESS Silness & Loe Plaque Index
By levels of TCOLOUR2 Total-Colour (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			.9095	.4708	461
TCOLOUR2	-1	Decrease	1.2428	.5549	65
TCOLOUR2	0	No Change	.8437	.4389	360
TCOLOUR2	1	Increase	.9658	.3468	36

F-stat = 21.88 ; P < .0001

Summaries of SILNESS Silness & Loe Plaque Index
By levels of TATTACH2 Total-Attachment (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			.9095	.4708	461
TATTACH2	-1	Decrease	1.0604	.4215	92
TATTACH2	0	No Change	.8680	.4993	250
TATTACH2	1	Increase	.8800	.4226	119

F-stat = 6.06 ; P = .0025

Summaries of OLEARY OLeary Plaque Index (%)
By levels of MBLEED2 Mesial-Bleeding (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			54.3586	25.1369	461
MBLEED2	-1	Decrease	62.5750	30.0701	56
MBLEED2	0	No Change	52.2414	23.8836	372
MBLEED2	1	Increase	64.2818	25.3725	33

F-stat = 7.06 ; P = .0010

Summaries of OLEARY OLeary Plaque Index (%)
By levels of FBLEED2 Facial-Bleeding (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			54.3586	25.1369	461
FBLEED2	-1	Decrease	76.5562	23.0771	16
FBLEED2	0	No Change	53.2212	24.9740	430
FBLEED2	1	Increase	63.2867	19.7597	15

F-stat = 7.85 ; P = .0004

Summaries of OLEARY OLeary Plaque Index (%)
By levels of DBLEED2 Distal-Bleeding (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			54.3586	25.1369	461
DBLEED2	-1	Decrease	62.4369	27.9649	65
DBLEED2	0	No Change	52.1208	23.8911	370
DBLEED2	1	Increase	66.0077	28.5408	26

F-stat = 7.84 ; P = .0004

Summaries of OLEARY OLeary Plaque Index (%)
By levels of MTONE2 Mesial-Tone (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			54.3586	25.1369	461
MTONE2	-1	Decrease	76.4294	33.6283	17
MTONE2	0	No Change	52.8830	24.3044	430
MTONE2	1	Increase	72.8786	19.8674	14

F-stat = 11.61 ; P < .0001

Summaries of OLEARY OLeary Plaque Index (%)
By levels of FTONE2 Facial-Tone (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			54.3586	25.1369	461
FTONE2	-1	Decrease	62.8333	22.7105	6
FTONE2	0	No Change	54.1803	25.1736	451
FTONE2	1	Increase	61.7500	27.3542	4

F-stat = 0.52 ; P = .59

Summaries of OLEARY OLeary Plaque Index (%)
By levels of DTONE2 Distal-Tone (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			54.3586	25.1369	461
DTONE2	-1	Decrease	79.0316	29.9740	19
DTONE2	0	No Change	52.8804	24.3388	429
DTONE2	1	Increase	67.0769	22.9872	13

F-stat = 12.12 ; P < .0001

Summaries of OLEARY OLeary Plaque Index (%)
By levels of MCOLOUR2 Mesial-Colour (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			54.3586	25.1369	461
MCOLOUR2	-1	Decrease	65.4442	31.9285	52
MCOLOUR2	0	No Change	52.4992	23.5361	399
MCOLOUR2	1	Increase	70.9000	29.2288	10

F-stat = 8.59 ; P = .0002

Summaries of OLEARY OLeary Plaque Index (%)
By levels of FCOLOUR2 Facial-Colour (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			54.3586	25.1369	461
FCOLOUR2	-1	Decrease	87.3333	22.2071	27
FCOLOUR2	0	No Change	52.0619	24.5114	409
FCOLOUR2	1	Increase	56.3200	6.7498	25

F-stat = 27.95 ; P < .0001

Summaries of OLEARY OLeary Plaque Index (%)
By levels of DCOLOUR2 Distal-Colour (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			54.3586	25.1369	461
DCOLOUR2	-1	Decrease	64.6760	33.0944	50
DCOLOUR2	0	No Change	52.7127	23.2279	402
DCOLOUR2	1	Increase	70.5556	38.5101	9

F-stat = 7.13 ; P = .0009

Summaries of OLEARY OLeary Plaque Index (%)
By levels of MATTACH2 Mesial-Attachment (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			54.3586	25.1369	461
MATTACH2	-1	Decrease	56.5045	25.2085	66
MATTACH2	0	No Change	54.4128	26.5886	327
MATTACH2	1	Increase	52.0147	16.4842	68

F-stat = 0.54 ; P = .59

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Summaries of     OLEARY     OLeary Plaque Index (%)
By levels of     FATTACH2   Facial-Attachment (categoric)
Variable      Value  Label                      Mean     Std Dev    Cases
For Entire Population                        54.3586    25.1369      461
FATTACH2         -1  Decrease                61.6706    26.0075       34
FATTACH2          0  No Change               54.2156    25.7887      366
FATTACH2          1  Increase                51.1410    19.6360       61
F-stat = 1.95 ; P = .14

Summaries of     OLEARY     OLeary Plaque Index (%)
By levels of     DATTACH2   Distal-Attachment (categoric)
Variable      Value  Label                      Mean     Std Dev    Cases
For Entire Population                        54.3586    25.1369      461
DATTACH2         -1  Decrease                52.7833    25.2271       42
DATTACH2          0  No Change               54.1201    26.3757      353
DATTACH2          1  Increase                56.6364    17.1951       66
F-stat = 0.37 ; P = .69

Summaries of     OLEARY     OLeary Plaque Index (%)
By levels of     TBLEED2    Total-Bleeding (categoric)
Variable      Value  Label                      Mean     Std Dev    Cases
For Entire Population                        54.3586    25.1369      461
TBLEED2          -1  Decrease                58.0792    27.5437       96
TBLEED2           0  No Change               51.7765    23.7314      311
TBLEED2           1  Increase                62.6148    26.3918       54
F-stat = 5.72 ; P = .0035

Summaries of     OLEARY     OLeary Plaque Index (%)
By levels of     TTONE2     Total-Tone (categoric)
Variable      Value  Label                      Mean     Std Dev    Cases
For Entire Population                        54.3586    25.1369      461
TTONE2           -1  Decrease                68.6036    31.5898       28
TTONE2            0  No Change               52.5100    24.2920      410
TTONE2            1  Increase                69.9696    20.9700       23
F-stat = 10.45 ; P < .0001

Summaries of     OLEARY     OLeary Plaque Index (%)
By levels of     TCOLOUR2   Total-Colour (categoric)
Variable      Value  Label                      Mean     Std Dev    Cases
For Entire Population                        54.3586    25.1369      461
TCOLOUR2         -1  Decrease                61.9538    30.9049       65
TCOLOUR2          0  No Change               52.4703    23.9072      360
TCOLOUR2          1  Increase                59.5278    22.8954       36
F-stat = 4.82 ; P = .0085

Summaries of     OLEARY     OLeary Plaque Index (%)
By levels of     TATTACH2   Total-Attachment (categoric)
Variable      Value  Label                      Mean     Std Dev    Cases
For Entire Population                        54.3586    25.1369      461
TATTACH2         -1  Decrease                56.2130    24.7941       92
TATTACH2          0  No Change               54.0928    28.2234      250
TATTACH2          1  Increase                53.4832    17.4537      119
F-stat = 0.34 ; P = .72
```

D. Attachment Loss vs. Max Opening

Note: Max Opening is recorded on a "per patient" basis, while attachment loss is recorded on a "per tooth" basis. One-way analysis of variance is used here.

Summaries of MAXOPEN1 Max Opening-start
By levels of MATTACH2 Mesial-Attachment (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			41.3949	10.5450	352
MATTACH2	-1	Decrease	40.1489	13.3856	47
MATTACH2	0	No Change	41.8517	9.9842	263
MATTACH2	1	Increase	39.9286	10.4213	42

F-stat = 0.98 ; P = .38

Summaries of MAXOPEN1 Max Opening-start
By levels of FATTACH2 Facial-Attachment (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			41.3949	10.5450	352
FATTACH2	-1	Decrease	40.6552	12.0720	29
FATTACH2	0	No Change	41.1644	9.7502	292
FATTACH2	1	Increase	44.2581	15.2752	31

F-stat = 1.29 ; P = .28

Summaries of MAXOPEN1 Max Opening-start
By levels of DATTACH2 Distal-Attachment (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			41.3949	10.5450	352
DATTACH2	-1	Decrease	37.1429	10.9940	28
DATTACH2	0	No Change	41.7250	10.3854	280
DATTACH2	1	Increase	42.0000	10.9140	44

F-stat = 2.51 ; P = .083

Summaries of MAXOPEN1 Max Opening-start
By levels of TATTACH2 Total-Attachment (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			41.3949	10.5450	352
TATTACH2	-1	Decrease	39.8806	12.6999	67
TATTACH2	0	No Change	41.5924	8.8509	211
TATTACH2	1	Increase	42.2027	12.6729	74

F-stat = 0.94 ; P = .39

Summaries of MAXOPEN2 Max Opening-end
By levels of MATTACH2 Mesial-Attachment (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			36.5909	7.7535	352
MATTACH2	-1	Decrease	32.6809	8.5213	47
MATTACH2	0	No Change	37.7757	7.5275	263
MATTACH2	1	Increase	33.5476	5.9231	42

F-stat = 13.13 ; P < .0001

Summaries of MAXOPEN2 Max Opening-end
By levels of FATTACH2 Facial-Attachment (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			36.5909	7.7535	352
FATTACH2	-1	Decrease	32.5172	7.5291	29
FATTACH2	0	No Change	37.5103	7.4278	292
FATTACH2	1	Increase	31.7419	8.1689	31

F-stat = 12.94 ; P < .0001

Summaries of MAXOPEN2 Max Opening-end
By levels of DATTACH2 Distal-Attachment (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			36.5909	7.7535	352
DATTACH2	-1	Decrease	32.5357	7.8951	28
DATTACH2	0	No Change	37.4714	7.7357	280
DATTACH2	1	Increase	33.5682	6.1810	44

F-stat = 9.41 ; P = .0001

```
Summaries of     MAXOPEN2   Max Opening-end
By levels of     TATTACH2   Total-Attachment (categoric)
Variable      Value  Label                      Mean     Std Dev     Cases
For Entire Population                         36.5909      7.7535       352
TATTACH2         -1  Decrease                 33.0746      8.3581        67
TATTACH2          0  No Change                39.0237      6.8871       211
TATTACH2          1  Increase                 32.8378      6.8347        74
F-stat = 30.27 ; P < .0001
```

E. Attachment Loss vs. Bleeding

Note: Both Attachment Loss and Bleeding are recorded a "per tooth" basis. Since they have been recoded to three categories, crosstabulations are constructed here.

MATTACH2 Mesial-Attachment (categoric) by MBLEED2 Mesial-Bleeding (categoric)

Count	MBLEED2 Decrease -1	No Change 0	Increase 1	Row Total
MATTACH2 Decrease -1	15	46	5	66
No Change 0	33	270	24	327
Increase 1	8	56	4	68
Column Total	56	372	33	461

Cohen's Kappa = .066

FATTACH2 Facial-Attachment (categoric) by FBLEED2 Facial-Bleeding (categoric)

Count	FBLEED2 Decrease -1	No Change 0	Increase 1	Row Total
FATTACH2 Decrease -1	4	27	3	34
No Change 0	11	346	9	366
Increase 1	1	57	3	61
Column Total	16	430	15	461

Cohen's Kappa = .073

DATTACH2 Distal-Attachment (categoric) by DBLEED2 Distal-Bleeding (categoric)

Count	DBLEED2 Decrease -1	No Change 0	Increase 1	Row Total
DATTACH2 Decrease -1	8	31	3	42
No Change 0	50	282	21	353
Increase 1	7	57	2	66
Column Total	65	370	26	461

Cohen's Kappa = -.006

TATTACH2 Total-Attachment (categoric) by TBLEED2 Total-Bleeding (categoric)

Count	TBLEED2 Decrease -1	No Change 0	Increase 1	Row Total
TATTACH2 Decrease -1	28	56	8	92
No Change 0	47	171	32	250
Increase 1	21	84	14	119
Column Total	96	311	54	461

Cohen's Kappa = .043

F. Attachment Loss vs. Tone

Note: Both Attachment Loss and Tone are recorded a "per tooth" basis. Since they have been recoded to three categories, crosstabulations are constructed here.

MATTACH2 Mesial-Attachment (categoric) by MTONE2 Mesial-Tone (categoric)

		MTONE2			
	Count	Decrease -1	No Change 0	Increase 1	Row Total
MATTACH2					
Decrease	-1	5	57	4	66
No Change	0	7	311	9	327
Increase	1	5	62	1	68
Column Total		17	430	14	461

Cohen's Kappa = .049

FATTACH2 Facial-Attachment (categoric) by FTONE2 Facial-Tone (categoric)

		FTONE2			
	Count	Decrease -1	No Change 0	Increase 1	Row Total
FATTACH2					
Decrease	-1	2	31	1	34
No Change	0	4	359	3	366
Increase	1		61		61
Column Total		6	451	4	461

Cohen's Kappa = .019

DATTACH2 Distal-Attachment (categoric) by DTONE2 Distal-Tone (categoric)

		DTONE2			
	Count	Decrease -1	No Change 0	Increase 1	Row Total
DATTACH2					
Decrease	-1	2	38	2	42
No Change	0	13	329	11	353
Increase	1	4	62		66
Column Total		19	429	13	461

Cohen's Kappa = -.008

TATTACH2 Total-Attachment (categoric) by TTONE2 Total-Tone (categoric)

		TTONE2			
	Count	Decrease -1	No Change 0	Increase 1	Row Total
TATTACH2					
Decrease	-1	7	77	8	92
No Change	0	12	228	10	250
Increase	1	9	105	5	119
Column Total		28	410	23	461

Cohen's Kappa = .027

G. Attachment Loss vs. Colour

Note: Both Attachment Loss and Colour are recorded a "per tooth" basis. Since they have been recoded to three categories, crosstabulations are constructed here.

MATTACH2 Mesial-Attachment (categoric) by MCOLOUR2 Mesial-Colour (categoric)

	MCOLOUR2			
Count	Decrease -1	No Change 0	Increase 1	Row Total
MATTACH2				
Decrease -1	12	51	3	66
No Change 0	40	281	6	327
Increase 1		67	1	68
Column Total	52	399	10	461

Cohen's Kappa = .012

FATTACH2 Facial-Attachment (categoric) by FCOLOUR2 Facial-Colour (categoric)

	FCOLOUR2			
Count	Decrease -1	No Change 0	Increase 1	Row Total
FATTACH2				
Decrease -1	5	25	4	34
No Change 0	22	333	11	366
Increase 1		51	10	61
Column Total	27	409	25	461

Cohen's Kappa = .137

DATTACH2 Distal-Attachment (categoric) by DCOLOUR2 Distal-Colour (categoric)

	DCOLOUR2			
Count	Decrease -1	No Change 0	Increase 1	Row Total
DATTACH2				
Decrease -1	8	33	1	42
No Change 0	41	305	7	353
Increase 1	1	64	1	66
Column Total	50	402	9	461

Cohen's Kappa = .002

TATTACH2 Total-Attachment (categoric) by TCOLOUR2 Total-Colour (categoric)

	TCOLOUR2			
Count	Decrease -1	No Change 0	Increase 1	Row Total
TATTACH2				
Decrease -1	20	62	10	92
No Change 0	43	197	10	250
Increase 1	2	101	16	119
Column Total	65	360	36	461

Cohen's Kappa = .064

H. Quality of Life vs. Attachment Loss

Note: Quality of Life is recorded on a "per patient" basis, while attachment loss is recorded on a "per tooth" basis. One-way analysis of variance is used here.

Summaries of QOL1 Quality of Life - start
By levels of MATTACH2 Mesial-Attachment (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			69.8850	17.3643	461
MATTACH2	-1	Decrease	72.1515	16.9227	66
MATTACH2	0	No Change	69.3547	17.4140	327
MATTACH2	1	Increase	70.2353	17.6137	68

F-stat = 0.73 ; P-value = .48

Summaries of QOL1 Quality of Life - start
By levels of FATTACH2 Facial-Attachment (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			69.8850	17.3643	461
FATTACH2	-1	Decrease	73.8824	16.9576	34
FATTACH2	0	No Change	70.5191	16.5181	366
FATTACH2	1	Increase	63.8525	21.0988	61

F-stat = 4.91 ; P-value = .0078

Summaries of QOL1 Quality of Life - start
By levels of DATTACH2 Distal-Attachment (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			69.8850	17.3643	461
DATTACH2	-1	Decrease	74.5952	14.5637	42
DATTACH2	0	No Change	69.4419	17.0446	353
DATTACH2	1	Increase	69.2576	20.2722	66

F-stat = 1.71 ; P-value = .18

Summaries of QOL1 Quality of Life - start
By levels of TATTACH2 Total-Attachment (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			69.8850	17.3643	461
TATTACH2	-1	Decrease	73.3043	17.1936	92
TATTACH2	0	No Change	69.5800	15.5982	250
TATTACH2	1	Increase	67.8824	20.5101	119

F-stat = 2.63 ; P-value = .073

Summaries of QOL2 Quality of Life - end
By levels of MATTACH2 Mesial-Attachment (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			66.0499	20.7287	461
MATTACH2	-1	Decrease	69.3939	17.0564	66
MATTACH2	0	No Change	65.3609	21.1784	327
MATTACH2	1	Increase	66.1176	21.7273	68

F-stat = 1.04 ; P-value = .35

Summaries of QOL2 Quality of Life - end
By levels of FATTACH2 Facial-Attachment (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			66.0499	20.7287	461
FATTACH2	-1	Decrease	74.2059	18.8161	34
FATTACH2	0	No Change	66.1175	20.9092	366
FATTACH2	1	Increase	61.0984	19.4222	61

F-stat = 4.44 ; P-value = .012

Summaries of QOL2 Quality of Life - end
By levels of DATTACH2 Distal-Attachment (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			66.0499	20.7287	461
DATTACH2	-1	Decrease	74.2857	15.9210	42
DATTACH2	0	No Change	65.4504	20.7276	353
DATTACH2	1	Increase	64.0152	22.4564	66

F-stat = 3.84 ; P-value = .023

Summaries of QOL2 Quality of Life - end
By levels of TATTACH2 Total-Attachment (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			66.0499	20.7287	461
TATTACH2	-1	Decrease	70.9130	18.3187	92
TATTACH2	0	No Change	65.6720	20.7921	250
TATTACH2	1	Increase	63.0840	21.8258	119

F-stat = 3.84 ; P-value = .022

Summaries of QOLD Quality of Life - difference
By levels of MATTACH2 Mesial-Attachment (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			-3.8351	20.2491	461
MATTACH2	-1	Decrease	-2.7576	15.6815	66
MATTACH2	0	No Change	-3.9939	19.7661	327
MATTACH2	1	Increase	-4.1176	25.9647	68

F-stat = 0.11 ; P-value = .90

Summaries of QOLD Quality of Life - difference
By levels of FATTACH2 Facial-Attachment (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			-3.8351	20.2491	461
FATTACH2	-1	Decrease	.3235	13.4631	34
FATTACH2	0	No Change	-4.4016	20.8817	366
FATTACH2	1	Increase	-2.7541	19.4496	61

F-stat = 0.95 ; P-value = .39

Summaries of QOLD Quality of Life - difference
By levels of DATTACH2 Distal-Attachment (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			-3.8351	20.2491	461
DATTACH2	-1	Decrease	-.3095	11.9133	42
DATTACH2	0	No Change	-3.9915	20.1067	353
DATTACH2	1	Increase	-5.2424	24.7523	66

F-stat = 0.81 ; P-value = .45

Summaries of QOLD Quality of Life - difference
By levels of TATTACH2 Total-Attachment (categoric)

Variable	Value	Label	Mean	Std Dev	Cases
For Entire Population			-3.8351	20.2491	461
TATTACH2	-1	Decrease	-2.3913	14.7365	92
TATTACH2	0	No Change	-3.9080	20.3372	250
TATTACH2	1	Increase	-4.7983	23.5709	119

F-stat = 0.37 ; P-value = .69