DISTRIBUTION OF SYSTEMIC MACROLIDES TO GINGIVA CREVICULAR FLUID: EFFECT ON CREVICULAR FLUID FLOW

MASTERS THESIS

Presented in Partial Fulfillment of Requirements for the Degree Master of Science in Dentistry in the Graduate School of The Ohio State University

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2009

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ABSTRACT

Objective: Azithromycin and other macrolides have been shown to produce antimicrobial and anti-inflammatory effects when used to treat chronic inflammatory airway diseases. Azithromycin produces potent inhibition of *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis* and *Prevotella intermedia*, and previous studies suggest that azithromycin improves non-surgical periodontal therapy outcomes in patients with chronic and aggressive periodontitis or drug-induced gingival enlargement. Macrolides distribute to gingiva at concentrations higher than those found in blood serum. They are taken up and accumulated by gingival fibroblasts, epithelial cells and phagocytes, which serve as reservoirs that buffer and sustain their therapeutic concentrations in the gingiva. It is unclear whether macrolides produce anti-inflammatory effects in the gingiva, but it is feasible that azithromycin can decrease the rate of gingival crevicular fluid (GCF) flow by decreasing the level of inflammatory mediators in GCF.

Methods: Ten healthy volunteers in good periodontal health were administered an initial 500 mg dose of azithromycin followed by 250 mg doses 24 and 48 hours later. GCF samples were collected from twelve maxillary posterior interproximal sites on day 0 (prior to the first dose of azithromycin) and on days 2, 4, 7, 14 after the first dose. GCF samples were collected with paper strips for 30 seconds and measured with a gingival fluid meter. The paper strips were pooled and stored in sealed vials in liquid nitrogen.
At the time for cytokine analysis, GCF samples were eluted from paper strips in 200 µl of Hanks balanced salts solution. A commercially available multiplex cytokine immunoassay was used to measure the content of IL-1β, IL-8, TNF-α, VEGF, IL-6 and IL-10.

Results: Azithromycin had significant treatment effects on pooled GCF volume as well as the amount of IL-1β, VEGF, TNF-α and IL-8 measured in GCF over time (P < 0.005). Significant decreases in pooled GCF volume were evident on days 2, 4 and 7 (P < 0.05). GCF volume increased after day 7 and was not significantly different from baseline on day 14. Azithromycin triggered a significant decrease in GCF IL-1β content relative to baseline on days 2, 4, 7 and 14. In comparison to baseline levels, VEGF content was significantly lower on days 2, 4 and 7, while TNF-α content was significantly lower on days 4 and 7. IL-8 content decreased from baseline levels on days 2, 4 and 7, but the difference was statistically significant only on day 4. IL-6 and IL-10 were not detected in GCF samples obtained from healthy gingiva in this population. The median Gingival Index and Plaque Index values were 0 throughout the study period.

Conclusions: Azithromycin induces significant decreases in GCF volume and biological mediator content at healthy periodontal sites that were essentially free of bacterial plaque. This suggests it has potent anti-inflammatory effects in addition to its known antimicrobial effects. The close temporal relationship between the decreases in GCF volume and GCF pro-inflammatory cytokine content suggests that azithromycin effects on GCF volume could be mediated by inhibition of cytokine production.
DEDICATION

This is dedicated to my mother and sisters for their patience and understanding in the past 3 years, my best friends Ernest and Aaron for their unselfish help, and my fellow residents for being around when I needed support.
ACKNOWLEDGEMENTS

I would like to thank my advisor, Dr. Walters, for his guidance. I would like to thank my Master’s committee for their advice and assistance. Also, I would like to thank my fellow residents for all their help throughout the entire project. This work was supported by United States Public Health Service grant R21 DE018804.
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FIELDS OF STUDY

Major Field: Periodontics
TABLE OF CONTENTS

Abstract ...........................................................................................................ii
Dedication .....................................................................................................iv
Acknowledgements ......................................................................................v
Vita ................................................................................................................vi
Table of Contents .........................................................................................vii
List of Tables ...............................................................................................viii
List of Figures ..............................................................................................ix
Chapter 1 Introduction ................................................................................1
Chapter 2 Materials and Methods ...............................................................5
Chapter 3 Results ........................................................................................9
Chapter 4 Discussion ..................................................................................18
List of References ......................................................................................22
LIST OF TABLES

Table 1: ........................................................................................................8
Table 2: .....................................................................................................11
Table 3: .....................................................................................................12
Table 4: .....................................................................................................14
Table 5: .....................................................................................................16
LIST OF FIGURES

Figure 1: ..................................................................................13
Figure 2: ..................................................................................15
Figure 3: ..................................................................................17
CHAPTER 1

INTRODUCTION

The purpose of mechanical debridement (scaling and root planing) in periodontal therapy is to remove bacterial plaque and bacterial products from root surfaces. While this approach is commonly used to arrest periodontal tissue breakdown, it is not always effective in eliminating the periodontal pathogens.[1] This is due to the tissue-invasive properties of certain subgingival periodontal pathogens. *Porphyromonas gingivalis* (P.g) and *Aggregatibacter actinomycetemcomitans* (A.a) are putative periodontal pathogens that can resist mechanical debridement by invading epithelial cells in periodontal pockets. Adjunctive systemic antimicrobial chemotherapy may help eliminate pathogens that can resist mechanical debridement.[2] The premise of antimicrobial periodontal therapy is based on the assumption that the antimicrobial agent in the periodontal pocket can surpass the concentration required to annihilate periodontal pathogens. Eradicating periodontal pathogens helps prevent future disease progression.[2]

Macrolide antimicrobials (e.g., erythromycin, azithromycin and clarithromycin) are known to attain high therapeutic concentrations in tissues.[3, 4] Azithromycin is potentially a good choice for eliminating periodontal pathogens due to its stability, bioavailability and spectrum of action.[5] Azithromycin is more effective against some periodontal pathogens (e.g., *Peptostreptococcus species, Porphyromonas gingivalis,*
*Prevotella intermedia* and *Aggregatibacter actinomycetemcomitans*) than erythromycin. [6-8] Compared with erythromycin, azithromycin has a broader antimicrobial spectrum, decreased breakdown in acid, increased tissue penetration, a lower incidence of adverse side effects and a longer half-life.[9] Azithromycin inhibits protein biosynthesis at the 50S subunit of the bacterial ribosome. Azithromycin is actively transported by polymorphonuclear leukocytes, fibroblasts, monocytes and alveolar macrophages and produces higher intracellular concentrations in those cells.[10, 11] The higher intracellular concentration of azithromycin makes it more effective against intracellular pathogens such as *Staphylococcus aureus, Legionella pneumophila, Chlamydia trachomatis* and *Salmonella typhi*. [12, 13] Several studies reported that macrolides are taken up by gingival fibroblasts, epithelial cells and phagocytes, which could potentially serve as antibiotic “reservoirs” that buffer and sustain their therapeutic concentrations in the gingiva.[14-16] Previous studies have shown that azithromycin can improve clinical treatment outcomes in patients with chronic periodontitis, aggressive periodontitis and drug-induced gingival enlargement.[17-20]

Macrolide antimicrobials are also effective for the treatment of bronchiolitis obliterans syndrome[21], chronic bronchitis and diffuse panbronchiolitis, cystic fibrosis[22], and other chronic inflammatory airway diseases [23]. The efficacy of macrolide antibiotics in treating chronic inflammatory airway diseases appears to involve inhibition of pro-inflammatory cytokine production as well as antimicrobial effects.[24, 25] Macrolides have been shown to decrease several inflammatory mediators including interleukin-8 (IL-8)[26], tumor necrosis factor-α (TNF-α), and leukotriene B₄ (LTB₄) produced by bronchial epithelial cells in vitro and thus enhance the clinical effectiveness of the
antibiotics.[27] However, there have been no previous studies to determine whether macrolides inhibit the production of inflammatory mediators in gingival tissue.

Gingival crevicular fluid (GCF) is a complex mixture which includes bacterial byproducts, inflammatory mediators, host derived enzymes and tissue breakdown products.[28] The rate of GCF flow is strongly correlated with histological signs of gingival inflammation. In the presence of gingivitis and periodontitis, GCF is expressed at a relatively high rate of flow and exhibits characteristics of an inflammatory exudate.[29] In healthy gingiva, GCF is a transudate of gingival tissue interstitial fluid and its flow rate is relatively low. Clinically healthy gingiva exhibits histological signs of low-level inflammation.[30-32] Thus, it is feasible that drugs which produce anti-inflammatory effects in the gingiva could induce a reduction in GCF flow even at clinically healthy sites. A previous study provides indirect evidence that clarithromycin (a macrolide related to azithromycin) can induce a reduction in the rate of GCF flow.[14]

From previous studies, levels of vascular endothelial growth factor (VEGF) and pro-inflammatory cytokines IL-1β, TNFα, IL-6 and IL-8 decrease in response to periodontal scaling and root planing. When tissue inflammation decreases, GCF flow rate, VEGF and pro-inflammatory cytokines content in GCF also decrease.[33-36]

We hypothesize that azithromycin decreases the production of VEGF and pro-inflammatory cytokines IL-1β, TNFα, IL-6, IL-8 in clinically healthy gingiva, triggering
a reduction in the rate of GCF flow. We further hypothesize that azithromycin may increase the production of the anti-inflammatory cytokine IL-10. In the present report, we address this hypothesis with a prospective human clinical study.
CHAPTER 2

MATERIALS AND METHODS

Subjects: Ten healthy adult volunteers with no clinical periodontal attachment loss were recruited from the student population of the Ohio State University College of Dentistry. Subjects with systemic disease, a history of a drug allergy or a history of use of any medications in the 2 weeks prior to the study were excluded. Females who were pregnant or lactating were also excluded. Informed consent was obtained under a protocol approved by the Institutional Review Board.

Study Design: The study design was a prospective longitudinal study (Table 1). All subjects were healthy with no clinical periodontal attachment loss. Each subject received a prophylaxis and oral hygiene instructions (including interproximal flossing and toothbrushing) one week before azithromycin was administered. Subjects were administered a regimen of azithromycin for three days (500 mg first day, then 250 mg per day for the following two days) to establish steady-state levels in gingiva. The subjects were given a form and asked to document the times and dates they took the medication. The Plaque Index (PI)[37] and the Gingival Index (GI)[38] were determined for each subject on study day 0 (baseline) and every subsequent appointment. GCF samples were obtained on day 0 (before the first dose of azithromycin) and on days 2, 4, 7 and 14 after the first dose. GI and PI were recorded from 12 maxillary posterior interproximal sites.
Gingival crevicular fluid samples were obtained from the same 12 maxillary interproximal sites, using filter paper strips\(^\text{\textcopyright}\) as previously described [39]. Briefly, the site was isolated with cotton rolls and the teeth and gingival tissues were gently air dried to avoid contamination with saliva. GCF samples were collected by positioning paper strips at the orifice of the crevice for 30 seconds from 12 maxillary mesially interproximal sites. GCF sample volume was measured with Periotron 6000\(^\text{\textcopyright}\) that had been calibrated by an established method [40]. The paper strips from individual subjects then were pooled and stored in sealed vials in liquid nitrogen until time for cytokine analysis.

**Sample preparation and analysis:** Paper strips containing the pooled GCF samples were placed in a 0.5 ml microtube which had been modified with a small diameter perforation at its tip. The tube was placed inside a 1.5 ml microtube and a 200 µl aliquot of Hanks balanced salts solution (HBSS) was added. GCF was eluted from each pool of sample strips by incubation on ice for 20 minutes. The samples were eluted into the bottom of the larger tube by centrifugation at 6,000 x g for 1 minute. A 50 µl aliquot of each sample was used for assays of cytokine content. A commercially available multiplex bead-based cytokine immunoassay (BioPlex, BioRad Laboratories Inc)\(^\text{\texttrademark}\) was used to measure the content of interleukin-1\(\beta\) (IL-1\(\beta\)), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)) and vascular endothelial growth

\(^{\text{\textcopyright}}\) Periopaper\textsuperscript{\textregistered}, Oralfow Inc. Smithtown, NY, USA.

\(^{\text{\textcopyright}}\) Periotron 6000\textsuperscript{\textregistered}, IDE Interstate, Amityville, NY, USA.

\(^{\text{\texttrademark}}\) Bio-Plex\textsuperscript{\texttexttrademark} Cytokine Assay, Bio-Rad Laboratories, Inc.
factor (VEGF) according to the manufacturer’s directions. The results were expressed as the total amount (in picograms) recovered from each pool of twelve paper strips.

**Statistical analysis:** The clinical variables GCF volume, PI and GI were analyzed with the Friedman repeated measures ANOVA on ranks. GCF IL-1β and VEGF contents were analyzed by one way repeated measures ANOVA, while GCF IL-8 and TNF-α contents were analyzed using Friedman repeated measures ANOVA on ranks.
<table>
<thead>
<tr>
<th>Visit number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Required (minutes)</td>
<td>45</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Reference day</td>
<td>First visit, day -7</td>
<td>Day 0 (baseline)</td>
<td>Day 1</td>
<td>Day 2</td>
<td>Day 4</td>
<td>Day 7</td>
<td>Day 14</td>
</tr>
<tr>
<td>Visit agenda</td>
<td>Informed Consent, Dental prophylaxis, GI, PI.</td>
<td>Collect GCF before first dose, GI, PI.</td>
<td>GI, PI.</td>
<td>Collect GCF, GI, PI.</td>
<td>Collect GCF, GI, PI.</td>
<td>Collect GCF, GI, PI.</td>
<td>Collect GCF, GI, PI.</td>
</tr>
<tr>
<td>Azithromycin (AZI) dosage</td>
<td></td>
<td>First dose of 500 mg AZI</td>
<td>Second dose of 250 mg AZI</td>
<td></td>
<td>Final dose of 250 mg AZI</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Study timetable.
CHAPTER 3

RESULTS

**Subject information:** Demographic information is presented in Table 2. The subject population included 6 males and 4 females with a mean mean age of 30 years. None of the subjects exhibited clinical signs of inflammation. Periodontal attachment loss, if present, was only found at isolated sites and was less than 2 mm. All study subjects were compliant with the azithromycin regimen.

**Effect of azithromycin on GCF volume:** Azithromycin had a significant treatment effect on pooled GCF volume (Figure 1 and Table 3, P < 0.001, Friedman repeated measures ANOVA on ranks). After initiation of azithromycin therapy, a significant decrease in pooled GCF volume from baseline was observed on days 2, 4 and 7 after the first dose (P < 0.05, Dunn’s test). Over the next week, pooled GCF volume increased. By day 14, the volume had increased to 90% of baseline levels (difference not statistically significant from baseline). The median Gingival Index and Plaque Index values were 0 throughout the study period (Table 3).

**Effect of azithromycin on GCF cytokine and VEGF content:** IL-6 and IL-10 were not detected in GCF samples from any of the subjects (data not shown). However, azithromycin had a significant treatment effect on the amount of IL-1β, IL-8, TNF-α and VEGF recovered from pooled samples of GCF (P < 0.005, repeated measures ANOVA or
ANOVA on ranks). Overall, the content of all four mediators reached their lowest levels on day 4 and increased toward baseline levels on days 7 and 14 (Figures 2 and 3). In comparison to baseline levels, a significant decrease in GCF IL-1β content was observed on days 2, 4, 7 and 14 (Figure 2 and Table 4). VEGF content was significantly lower than baseline on days 2, 4 and 7 (Figure 2 and Table 4), while the content of TNF-α was significantly lower on days 4 and 7 (Figure 3 and Table 5). IL-8 content decreased from baseline levels on days 2, 4 and 7, but the difference was statistically significant only on day 4 (Figure 3 and Table 5).
<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>Mean age</th>
<th>Male:Female ratio</th>
<th>Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>30</td>
<td>6:4</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 2: Study Subjects Demographics
<table>
<thead>
<tr>
<th>Day (Days)</th>
<th>Pooled GCF Volume (µl)*#</th>
<th>Plaque Index*</th>
<th>Gingival Index*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (baseline)</td>
<td>0.99 (0.59 to 1.39)§</td>
<td>0 (0 to 1)</td>
<td>0 (0 to 0)</td>
</tr>
<tr>
<td>2</td>
<td>0.52 (0.19 to 1.04)§</td>
<td>0 (0 to 0)</td>
<td>0 (0 to 0)</td>
</tr>
<tr>
<td>4</td>
<td>0.51 (0.41 to 0.91)§</td>
<td>0 (0 to 0)</td>
<td>0 (0 to 0)</td>
</tr>
<tr>
<td>7</td>
<td>0.59 (0.33 to 1.01)§</td>
<td>0 (0 to 0)</td>
<td>0 (0 to 0)</td>
</tr>
<tr>
<td>14</td>
<td>0.89 (0.50 to 1.82)</td>
<td>0 (0 to 0)</td>
<td>0 (0 to 0)</td>
</tr>
</tbody>
</table>

Table 3: GCF Volume, Plaque Index and Gingival Index Observed at Study Visits.

*Data are presented as median and range observed in 10 subjects.

§In this column, differences in median values among the different dates are statistically significant (P < 0.001, Friedman Repeated Measures ANOVA on Ranks). Significant differences from baseline (P < 0.05, Dunn’s test) are denoted by §.
Figure 1: Pooled GCF sample volumes before, during and after administration of azithromycin. Arrows indicate the times azithromycin was administered. The data represent the mean (± SEM) pooled GCF volume collected from twelve different maxillary interproximal sites. Significant differences from baseline are denoted by * (P < 0.05, Dunn’s test).
<table>
<thead>
<tr>
<th>Day</th>
<th>IL-1β (pg)</th>
<th>VEGF (pg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>39.7 ± 8.45</td>
<td>40.0 ± 5.96</td>
</tr>
<tr>
<td>2</td>
<td>14.1 ± 2.66†</td>
<td>25.1 ± 4.16†</td>
</tr>
<tr>
<td>4</td>
<td>11.1 ± 2.63†</td>
<td>21.1 ± 2.14†</td>
</tr>
<tr>
<td>7</td>
<td>19.2 ± 3.97†</td>
<td>30.0 ± 3.99†</td>
</tr>
<tr>
<td>14</td>
<td>26.7 ± 6.08†</td>
<td>38.4 ± 4.18</td>
</tr>
</tbody>
</table>

Table 4. Amounts of Interleukin-1β and VEGF Recovered in Gingival Crevicular Fluid at Study Visits*

*Data represent the mean (± SEM) amount recovered from a pool of twelve paper strips used to collect GCF samples from separate maxillary interproximal sites for thirty seconds each. Significant differences were observed in both columns (P < 0.001, repeated measures ANOVA). Within each column, significant differences from baseline (P < 0.05, Holm-Sidak test) are denoted by †.
Figure 2: Effect of azithromycin on GCF IL-1β and VEGF content. Arrows indicate the times azithromycin was administered. Data represent the mean (± SEM) recovery from samples obtained from twelve separate maxillary interproximal sites. The treatment effects on IL-1β and VEGF content were significant (P < 0.001, repeated measures ANOVA). Significant differences from baseline IL-1β is denoted by * and significant differences from baseline VEGF content is denoted by # (P < 0.05, Holm-Sidak test).
<table>
<thead>
<tr>
<th>Day</th>
<th>IL-8 (pg)</th>
<th>TNF-α (pg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>99.4 ± 26.1</td>
<td>1.32 ± 0.325</td>
</tr>
<tr>
<td>2</td>
<td>62.5 ± 14.2</td>
<td>0.545 ± 0.148</td>
</tr>
<tr>
<td>4</td>
<td>31.9 ± 6.33†</td>
<td>0.341 ± 0.093†</td>
</tr>
<tr>
<td>7</td>
<td>67.2 ± 15.8</td>
<td>0.500 ± 0.128†</td>
</tr>
<tr>
<td>14</td>
<td>114 ± 24.4</td>
<td>0.805 ± 0.180</td>
</tr>
</tbody>
</table>

Table 5. Amounts of Interleukin-8 and TNF-α Recovered in Gingival Crevicular Fluid at Study Visits*  

*Data represent the mean (± SEM) amount recovered from a pool of twelve paper strips used to collect GCF samples from separate maxillary interproximal sites for thirty seconds each. Significant differences were observed in both columns (P < 0.005, Friedman repeated measures ANOVA on ranks). Within each column, significant differences from baseline (P < 0.05, Dunn’s test) are denoted by †.
Figure 3: Effect of azithromycin in GCF IL-8 and TNF-α content. Arrows indicate the times azithromycin was administered. Data represent the mean (± SEM) recovery in samples obtained from twelve separate maxillary interproximal sites. The treatment effects on IL-8 and TNF-α content were significant (P < 0.005, Friedman repeated measures ANOVA on ranks). Significant differences from baseline IL-8 content is denoted by # and significant differences from baseline TNF- α content is denoted by * (P < 0.05, Dunn’s test).
CHAPTER 4

DISCUSSION

The results of this study suggest that azithromycin produces anti-inflammatory effects in clinically healthy gingival tissues. The correlation of GCF flow rate with the severity of gingival inflammation is well documented in the literature. During experimental gingivitis, GCF flow rate increases significantly. When oral hygiene resumes and inflammation decreases, GCF flow rate also decreases.[41] The amount of GCF volume per strip found from clinically healthy gingiva in the present study was about 0.08 µl for a 30 second sample, which is in agreement with previous study by Darany et al.[42] The finding that azithromycin significantly decreases GCF flow rate at sites that are essentially plaque-free suggests that this effect is largely independent of its antimicrobial effects. These effects occurred rapidly (within 2 days of treatment), and GCF flow increased toward baseline levels as azithromycin was eliminated by the subjects. A previous report suggests that azithromycin concentrations decrease 80% in gingival tissues from day 4 to day 14.[43] The baseline levels of IL-1β, IL-8, and TNF-α observed in this study are reasonably similar to those reported in other studies of healthy human subjects.[44, 45]

Many host immune mediators have been identified in GCF. The pro-inflammatory cytokines IL-1β, IL-8 and TNF-α are involved in recruitment of inflammatory cells [46].
The total amount of these cytokines in GCF is related to the severity of inflammation. The IL-1β content in GCF from severe periodontitis sites is up to 2-fold higher than in samples from sites with mild to moderate disease. After scaling and root planing, the IL-1β content of GCF decreases significantly. While VEGF is not an inflammatory mediator, it plays an important role in angiogenesis and maintenance of periodontal health. The total amount of VEGF in GCF from periodontally diseased sites is greater than at healthy periodontal sites, and these levels reportedly decrease in response to periodontal therapy.

Despite use of a highly sensitive immunoassay, the pro-inflammatory cytokine IL-6 and anti-inflammatory cytokine IL-10 were not detected in any GCF samples collected in the present study. Considering that the subjects had healthy gingival tissues, this is not unexpected. IL-6, which induces B-cell maturation, regulates bone resorption and stimulates acute-phase protein production, is involved in the later stages of the inflammatory response when B-cells increase in number. IL-10 stimulates B-cell proliferation and inhibits production of many cytokines. It is likely that the levels of IL-6 and IL-10 levels are extremely low in the healthy gingival crevice.

Azithromycin treatment significantly decreased the amount of IL-1β, IL-8, TNF-α and VEGF in GCF in a manner that paralleled its effects on GCF flow rate. After a 3 day course of azithromycin, GCF flow rate and VEGF content from clinical healthy gingiva was significantly decreased on day 2, 4, and 7. On the other hand, the amount of IL-1β in GCF was significantly lower on day 2, 4, 7 and 14. TNF-α content in GCF was significantly decreased on day 4 and 7 while IL-8 content in GCF was lower on day 4.
The relationship between the decreases in GCF flow rate and GCF pro-inflammatory cytokine content suggests that azithromycin can produce anti-inflammatory effects even in clinically healthy gingiva. It is feasible that azithromycin effects on GCF volume could be mediated by inhibition of the production of one or more biological mediators produced by epithelium cells, fibroblasts, neutrophils and macrophages in the gingiva.

Although anti-inflammatory effects appear to contribute to the effectiveness of macrolides in treating chronic inflammatory airway diseases, [25] the mechanisms by which macrolides inhibit production of inflammatory mediators are not fully understood. Macrolides inhibit the activation of nuclear factor-κB (NF-κB) and activator protein-1 (AP-1) produced by bronchial epithelial cells, which are known to regulate the expression of IL-8, IL-6, TNF-α and IL-1β and other pro-inflammatory cytokines.[52, 53] Macrolides may also inhibit mitogen-activated protein kinase (MAPK) and extracellular-regulated kinase (ERK), resulting in a decrease in IL-8 production.[54] It is conceivable that azithromycin works through similar mechanisms to decrease the levels of IL-1β, IL-8, and TNF-α in GCF, but further study is needed to elucidate its effects on host cells in the gingiva.

The results support the hypothesis that azithromycin produces anti-inflammatory effects in gingiva. This characteristic of azithromycin, along with its antimicrobial and pharmacokinetic properties, is well suited for treatment of inflammatory periodontal diseases. Azithromycin is highly active against periodontal pathogens Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia and several other bacteria associated with periodontal diseases.[6-9] Azithromycin is used in a once-
daily regimen, which promotes patient compliance. It appears to localize in inflamed gingival tissues at levels that are significantly higher than in healthy gingiva. [15] For these reasons, it would be worthwhile to consider large-scale clinical trials to evaluate the adjunctive effects of azithromycin in treatment of aggressive, recurrent and chronic forms of periodontitis.
LIST OF REFERENCES


