Periodontal Therapy Reduces the Severity of Active Rheumatoid Arthritis in Patients Treated With or Without Tumor Necrosis Factor Inhibitors

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Background: Rheumatoid arthritis (RA) and periodontitis are common chronic inflammatory conditions. Recent studies showed a beneficial effect of periodontal treatment on the severity of active RA. This study was undertaken to further examine the effect of nonsurgical periodontal treatment on the signs and symptoms of RA in patients treated with or without anti-tumor necrosis factor-alpha (anti-TNF-α) medications. The effect of anti-TNF-α therapy on periodontitis also was assessed.

Methods: Forty participants diagnosed with moderate/severe RA (under treatment for RA) and severe periodontitis were randomly assigned to receive initial nonsurgical periodontal therapy with scaling/root planing and oral hygiene instructions (n = 20) or no periodontal therapy (n = 20). To control RA, all participants had been using disease-modifying anti-rheumatic drugs, and 20 had also been using anti-TNF-α before randomization. Probing depth (PD), clinical attachment level (CAL), bleeding on probing (BOP), gingival index (GI), plaque index (PI), RA disease activity score 28 (DAS28), and erythrocyte sedimentation rate (ESR) were measured at baseline and 6 weeks later. Linear mixed models were used to identify significant differences between subjects who received periodontal treatment and those who did not.

Results: Patients receiving periodontal treatment showed a significant decrease in the mean DAS28, ESR (P < 0.001), and serum TNF-α (P < 0.05). There was no statistically significant decrease in these parameters in patients not receiving periodontal treatment. Anti-TNF-α therapy resulted in a significant improvement in CAL, PD, BOP, and GI.

Conclusions: Non-surgical periodontal therapy had a beneficial effect on the signs and symptoms of RA, regardless of the medications used to treat this condition. Anti-TNF-α therapy without periodontal treatment had no significant effect on the periodontal condition. J Periodontol 2009;80:535-540.

KEY WORDS
Periodontitis; rheumatoid arthritis; therapy; tumor necrosis factor-alpha.

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder of unknown etiology that primarily involves joints. Periodontitis and RA share similar clinical and pathogenic characteristics.1-3 Clinically, both diseases are characterized by the local destruction of hard and soft tissues as a consequence of inflammation, and the pathogenesis includes the release of cytokines and matrix metalloproteinases (MMPs) from inflammatory cells.4-7 The expression of proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), leads to the propagation of inflammation and the release of high levels of inflammatory mediators that result in bone destruction.8 TNF-α inhibitors reduce the recruitment of inflammatory cells, osteoclast formation, and bone loss.9 Several studies10-18 suggested a relationship between RA and periodontitis; RA may have a negative impact on periodontal condition and vice versa. Mercado et al.12 reported a significantly high prevalence of moderate to severe periodontitis in individuals with RA. In addition, the converse is true: periodontitis patients have a higher prevalence of RA compared to the general population.12
Ramamurthy et al. found that induction of experimental arthritis in rats resulted in periodontal destruction and increased cytokines and MMPs in the periodontal tissues. Oral bacterial DNAs are detected in serum and synovial fluid of patients with RA. Patients with RA also have a significantly higher level of immunoglobulin G antibody against Porphyromonas gingivalis, Prevotella intermedia, and Tannerella forsythia (previously T. forsythensis). Furthermore, two recent clinical trials suggested that the treatment of periodontal disease might have a significant impact on RA severity. Similarly, subjects with RA have significantly increased periodontal attachment loss compared to controls, and oral hygiene may only partially account for the association.

Recently, TNF-α blocking agents have been developed and used for managing RA. Studies in animals and in humans suggested that anti-TNF-α therapy may reduce the severity of periodontitis. The present study was undertaken to evaluate the effect of periodontal therapy on serum TNF-α levels and the clinical status of patients with RA treated with or without TNF-α blocking agents. The effect of anti-TNF-α therapy on the periodontal condition of patients with RA was also evaluated.

**MATERIALS AND METHODS**

**Participants**

This study was conducted from February 4 to November 20, 2007; written informed consent was obtained from all subjects prior to their enrollment. The study was approved by the Institutional Review Board of University Hospitals Cleveland/Case Medical Center (No. 10-06-41 on January 24, 2007).

Inclusion criteria were age ≥30 years, confirmed diagnosis of active RA, generalized severe chronic periodontitis, and ≥20 teeth present. Exclusion criteria were antibiotic use during the 3 months prior to the study, smoking, diabetes, severe xerostomia, and pregnancy.

Forty subjects, recruited from the Rheumatology Division, University Hospitals of Cleveland, were enrolled. Of these, 20 subjects were taking disease-modifying antirheumatic drugs (DMARDs) alone and the other 20 subjects were on a combination of DMARDs and anti-TNF-α medication for management of their RA. Each of these groups of 20 participants was randomized to the treatment (n = 10) or control (n = 10) group. This resulted in the following four groups (10 subjects each): periodontal treatment only (group A), no periodontal treatment and no anti-TNF-α drug (group B), periodontal treatment and anti-TNF-α drug (group C), and anti-TNF-α drugs only (group D). DMARDs consisted of the following: methotrexate, hydroxychloroquine, leflunomide, and sulfasalazine, whereas anti-TNF-α drugs included infliximab, etanercept, and adalimumab. The dosages of the previous medications were determined by the treating rheumatologist based on the patients’ needs.

**Data Collection**

The following information was obtained from the subjects’ medical records: age, gender, medical history, and medications used by the subjects. Periodontal and RA status, as well as serum TNF-α level, were assessed at baseline and 6 weeks thereafter. The following data were recorded by a calibrated examiner to assess periodontal status: probing depth (PD) and clinical attachment level (CAL) at six sites per tooth, gingival index (GI) of Löe and Silness, plaque index (PI) of Löe, percentage of sites with bleeding on probing (BOP), and number of teeth present. To assess RA status, the following data were abstracted from the patients’ records: number of tender joints (TJs) and swollen joints (SJ), patients’ general assessment of their condition scored on a visual analog scale (VAS), erythrocyte sedimentation rate (ESR), and disease activity score 28 joints (DAS28). DAS28 is a numeric index that was introduced and validated in 1995. DAS28 score is calculated using TJ, SJ, VAS, and ESR. It is a widely used method for the assessment of RA disease activity in daily practice. To assess TNF-α, 2 ml blood was drawn at each visit, and enzyme-linked immunosorbent assay was used for TNF-α analysis. Subjects in the periodontal treatment groups (A and C) received oral hygiene instructions along with full-mouth scaling/root planing immediately after the baseline assessment. Participants in the control groups (B and D) were scheduled for periodontal treatment after completion of the study.

**Statistical Analyses**

The characteristics of the study participants (age, gender, and RA severity) were compared among the groups using the Kruskal-Wallis and χ² tests. Differences in PD, CAL, PI, and GI among the groups were compared using linear mixed models adjusted for age, gender, rheumatoid factor (RF), tooth type, and random effect from patients. The analyses were performed using the average values from each tooth. For BOP, the difference in the percentage of bleeding sites was calculated for each subject, and a linear regression model adjusted for age, gender, and RF was used to examine within-group differences. Linear regression models adjusted for age and gender were used to compare the intragroup differences in ESR and DAS28. The differences in the TNF-α level within each group from baseline to 6 months was tested using a two-sided paired t test. Linear mixed models, adjusted for baseline values, age, gender, RF, tooth type, and random effect from patients, were used to examine the intergroup differences in PD, CAL, PI, and GI.
A linear regression model adjusted for baseline values, age, gender, and RF was used to compare BOP among the groups. Linear regression models adjusted for baseline values, age, and gender were used to compare differences in ESR and DAS28 among the groups. The effect of periodontal treatment or anti-TNF-α treatment on RA were assessed from linear mixed models and linear models with dichotomous variables indicating whether the patient received periodontal treatment or anti-TNF-α treatment. Linear mixed models were fitted using a statistical procedure in software.

RESULTS

The distribution of the baseline variables (age, gender, and RA severity) is given in Table 1. There was a significant difference in the age of the patients among the four groups: groups A and D had older patients compared to groups B and C. No differences were found among the groups with regard to gender or RA severity.

Table 2 presents the differences in periodontal and RA parameters at baseline and 6 weeks. Subjects receiving periodontal therapy (groups A and C) showed a statistically significant improvement in ESR, DAS28, PD, BOP, PI, and GI when pre- and post-treatment visits were compared. No significant changes between the visits were observed in the control groups (groups B and D). When subjects receiving periodontal therapy (groups A and C) were compared to the control subjects (groups B and D), statistically significant differences in DAS28, PD, CAL, BOP, PI, and GI were observed among the groups (P<0.01), whereas ESR was not significantly different among the groups (P = 0.64). When subjects on the anti-TNF-α therapy (groups C and D) were compared to those not receiving TNF-α therapy (groups A and B), ESR, PD, CAL, BOP, and GI were significantly different among the groups (P<0.05). DAS28 and PI were not significantly different between those receiving TNF-α therapy or not (P>0.05).

Subjects receiving periodontal therapy (groups A and C) showed a statistically significant decrease in the number of SJs and VAS values after periodontal therapy. Subjects in group C also showed a statistically significant decrease in the number of TJs after periodontal therapy. No improvement in SJs, TJs, or VAS was seen in groups B and D. Subjects receiving periodontal therapy (groups A and C) showed a significant improvement in SJs (P<0.001), TJs (P = 0.2), and VAS (P<0.001) compared to the control subjects (groups B and D). These parameters were not significantly different between those treated with or without anti-TNF-α drugs (P>0.05). Table 3 presents the number of subjects showing a decrease in the serum TNF-α level between baseline and 6 weeks. Fifty percent of the subjects in group A and 40% of those in group C showed a decrease in serum TNF-α levels after periodontal treatment, whereas only 20% of the subjects in groups B and D showed such a decrease. The decrease in the mean TNF-α level between baseline (77.79 ± 53.99 pg/ml) and 6 weeks (42.48 ± 42.95 pg/ml) was statistically significant (P<0.001) in the periodontally treated subjects (groups A and C). In the control subjects (groups B and D), the difference was insignificant (P = 0.2); the mean TNF-α level at baseline and 6 weeks was 37.13 ± 39.94 and 77.89 ± 93.59, respectively.

DISCUSSION

Non-surgical periodontal treatment of subjects with moderate/severe chronic periodontitis and RA reduced the severity of RA as measured by disease activity score (DAS28). An improvement in ESR, number of SJs and TJs, and VAS also was observed in periodontally treated subjects. No such improvement was seen in
untreated controls. The difference between periodontally treated and non-treated subjects was statistically significant. These findings are in agreement with previous studies\(^{16,17}\) that suggest a beneficial effect of periodontal therapy on RA status. They also support the concept that periodontal disease is a systemic inflammatory condition.\(^{25-28}\) Periodontal treatment was shown to decrease systemic inflammatory products.\(^{29}\) Thus, the improvement in RA status after periodontal therapy might be attributed to a reduction in these markers. Another possible explanation is that elimination of periodontal pathogens by scaling and root planing reduces exposure of the joint structures to bacteria and their toxins, which leads to improved RA status.\(^{30}\)

Subjects on anti-TNF-\(\alpha\) therapy showed a statistically significant improvement in ESR, CAL, PD, BOP, and GI compared to those not receiving this therapy. This is consistent with findings of a previous study\(^{21}\) in subjects with RA that showed an inverse association between the use of anti-TNF-\(\alpha\) therapy and the severity of periodontitis. However, the severity of RA, as measured by DAS28, was not significantly different in subjects treated with or without anti-TNF-\(\alpha\) drugs. This could be attributed, in part, to the prolonged use of anti-TNF-\(\alpha\) therapy before initiation of the study.

Table 2.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAL (mm)</td>
<td>3.53 (0.99)</td>
<td>3.40 (0.88)</td>
<td>3.44 (1.03)</td>
<td>3.47 (1.00)</td>
<td>3.82 (1.11)</td>
</tr>
<tr>
<td>PD (mm)</td>
<td>3.06 (0.80)</td>
<td>2.85 (0.65)*</td>
<td>3.01 (0.71)</td>
<td>3.01 (0.69)</td>
<td>3.25 (0.70)</td>
</tr>
<tr>
<td>BOP (n sites)</td>
<td>0.83 (1.11)</td>
<td>0.63 (0.93)‡</td>
<td>0.75 (0.03)</td>
<td>0.81 (1.01)</td>
<td>1.72 (1.98)</td>
</tr>
<tr>
<td>GI</td>
<td>0.71 (0.49)</td>
<td>0.61 (0.43)‡</td>
<td>0.59 (0.44)</td>
<td>0.62 (0.42)</td>
<td>0.92 (0.67)</td>
</tr>
<tr>
<td>PI</td>
<td>1.09 (0.84)</td>
<td>0.80 (0.68)‡</td>
<td>0.82 (0.51)</td>
<td>0.87 (0.51)</td>
<td>1.17 (0.90)</td>
</tr>
</tbody>
</table>

* P <0.05, baseline versus 6 weeks.
† P <0.01, baseline versus 6 weeks.
‡ P <0.001, baseline versus 6 weeks.

Table 3.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>B</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>C</td>
<td>4</td>
<td>40</td>
</tr>
<tr>
<td>D</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>32.5</td>
</tr>
</tbody>
</table>

Frequency and Percentage of Patients With a Decrease in TNF-\(\alpha\)
CONCLUSION
The present findings indicate that control of periodontal infection and inflammation by means of scaling and root planing and oral hygiene in subjects with moderate to severe periodontal disease might contribute to a reduction in the signs and symptoms of active RA as well as to a reduction in the serum levels of TNF-α.

ACKNOWLEDGMENTS
This study was sponsored by the Department of Periodontics, Case Western Reserve University. The authors report no conflicts of interest related to this study.

REFERENCES
31. Wang Y, Yang PS, Qi XM, Ren JM, Ge SH. Change of circulating TNF-alpha in patients with advanced


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Submitted August 26, 2008; accepted for publication December 16, 2008.