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*J Immunol* 2004; 173:3514-3523; doi: 10.4049/jimmunol.173.5.3514

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The present study tested the effects of local injection of IL-1 and TNF soluble receptors on a periodontal wound-healing model in nonhuman primates. In this model, periodontal lesions were developed for 16 wk, followed by open flap surgery. Starting at the time of surgery, groups of animals received localized injections of both soluble cytokine receptors or else PBS three times per week for 3, 14, or 35 days. Periodontal wound healing was analyzed for each group at the end of the treatment regimen. Fourteen days after surgery, a significant decrease was observed between the animals treated with soluble receptors and the untreated group with respect to recruitment of inflammatory cells in deep gingival connective tissue. Concurrent apoptosis of inflammatory cells in those tissues increased significantly in treated animals compared with untreated animals. All other outcome parameters of periodontal wound healing were likewise significantly improved in treated animals compared with untreated animals. In marked contrast, however, 35 days after surgery, there was a significant increase in the number of inflammatory cells that had infiltrated into deep gingival connective tissue in treated compared with untreated animals. Outcome parameters of periodontal wound healing worsened in treated animals when compared with untreated. These results indicate that proinflammatory cytokines may play different functional roles in early vs late phases of periodontal wound healing. Short-term blockade of IL-1 and TNF may facilitate periodontal wound healing, whereas prolonged blockade may have adverse effects.

Received for publication September 25, 2003. Accepted for publication June 4, 2004.

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1 This work was supported by National Institute of Dental Research Grants DE12482 and DE11254.

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3 Abbreviations used in this paper: sIL, soluble IL; CRJ, crown-root junction; sTNFR, soluble TNFR; TRAP, tartrate-resistant acid phosphatase.
with an extended \( \frac{1}{2} \). One such fusion protein of the p75 sTNFR and the Fc portion of human IgG1 (etanercept) is now commercially available for treating rheumatoid arthritis (36), ankylosing spondylitis (37), and psoriasis (38).

Because inflammation is the initial phase of wound healing, we applied the same logic of interfering with IL-1 and TNF effects in this phase of wound healing (2) in hopes of improving outcomes in a well-defined nonhuman primate model of periodontal wound healing. We administered soluble receptors for IL-1 and TNF to block IL-1 and TNF functions, and then evaluated wound-healing outcomes. Our results suggest that IL-1 and TNF play distinct roles in different phases of periodontal wound healing. We conclude that short-term inhibition of these two cytokines might improve periodontal wound healing, whereas prolonged treatment would most likely delay it.

Materials and Methods

Reagents

sIL-1RI (consisting of the extracellular portion of the IL-1RI) and the chimeric soluble receptor to TNF (sTNFR:Fc, consisting of the extracellular domain of TNFRII linked to the Fc portion of a human IgG1) were generously provided by Amgen (Thousand Oaks, CA). Dosing of sIL-1RI (6 µg/injection) and of sTNFR:Fc (6 µg/injection) and administration frequencies were based upon our previous experience (39).

Periodontal wound-healing model

To minimize potential estrogen effects, 21 adult male Macaca mulatta were used in accordance with the protocol and procedures that had been approved by the Institutional Animal Care And Use Committee at the Boston University Medical Center. The animals used in this study were sedated with ketamine hydrochloric acid for all procedures. In addition, i.v. pentobarbital sodium was used during all surgical procedures. The temporal sequence of this model and the experimental design used in the present study are shown in Fig. 1. Maxillary palatal periodontal defects were produced, as described previously by Caton et al. (40), Amar et al. (41), and Karatzas et al. (42). After an 8-wk quarantine period, intrasulcular incisions were made on the palatal aspect of the maxilla and extended from the canine to the second maxillary molar in that quadrant. Mucoperiosteal flaps were retracted to expose the underlying bone, and under sterile saline irrigation osseous defects were surgically created by removing 5 mm alveolar bone from the crown-root junction (CRJ) in the corono-apical direction to expose the upper portion of the palatal roots of the two premolars and the first and second molars, extending well interproximally. Root surfaces were scaled and root planed to remove the exposed periodontal ligament and surface cementum. Identical lesions were produced on the contralateral teeth. To prevent spontaneous tissue regeneration, each of the involved eight teeth was fitted with a stainless steel band with a finger-like projection extending on the root exposure, and cemented to crown of the
To mimic human periodontal disease, we enhanced plaque accumulation by tying dental plaque-retentive silk ligatures around each tooth, and the flaps were sutured. Six weeks after surgery, the bands were removed and the silk ligatures were replaced to enhance bacterial plaque accumulation on the root surface. After another 6 wk, all silk ligatures were removed. Similar to the standard periodontal care and to obtain clinically healthy gingival condition, an oral hygiene program that consisted of tooth brushing with an antimicrobial (2% chlorhexidine) three times per week was started and continued for the whole duration of the study until tissues were harvested from the animals. Four weeks after the onset of oral hygiene procedures, surgical tissue blocks containing two premolars and the first and second molars with all surrounding tissues (referred as a maxillary block) from both sides (left and right) were dissected en bloc from each of three randomly selected animals. These specimens served as pretreatment controls (baseline controls). Open flap periodontal surgery was performed on the remaining 18 animals. First, inflammatory granulation tissue was carefully debrided. The exposed root surfaces were thoroughly root planed, and the apical extent of root planing was marked by the creation of a notch on the tooth surface. This landmark was used in histologic sections to differentiate newly formed tissues (cementum, bone) from pre-existing tissues. The flaps were then secured with 3.0 silk sutures. Animals were randomly assigned to the experimental (9 animals) or untreated groups (9 animals). For each group, 9 animals were randomly assigned to day 3 (3 animals), day 14 (3 animals), or day 35 (3 animals) time group.

**Treatment with soluble receptors**

As shown in Fig. 2, three animals per time point received IL-1/TNF inhibitors, while three received vehicle alone. Treatment with soluble receptors or vehicle was by local injection into the gingiva adjacent to each periodontal defect. Each injection consisted of 12 μg of soluble receptors (6 μg/injection sIL-1RI plus 6 μg/injection sTNFR:Fc) in 50 μl of sterile PBS or sterile PBS alone. Each animal received one set of injections (8 local injections = 4 injections per quadrant × 2 quadrants) three times per week. Thus, the number of sets of injections per animals was 2 for day 3 animals, 6 for day 14 animals, and 15 for day 35 animals. At the end of each time point, maxillary blocks, including the alveolar bone, periodontal ligament, and teeth, were surgically harvested.

**Tissue specimen preparation**

Maxillary blocks were immediately fixed in 4% paraformaldehyde in PBS for 2 days at 4°C. After fixation, specimens were washed and decalcified in 14.5% EDTA/glycerol (pH 7.1) for 14 wk with constant stirring at 4°C (39). After decalcification, each maxillary block was further dissected to provide four individual tooth blocks that included all surrounding periodontal tissues. Tooth blocks were paraffin embedded, and sectioning was performed on a buccal-lingual plane parallel to the long axis of the root. Serial 6-μm sections were prepared and stained with H&E, or with tartrate-resistant acid phosphatase (TRAP) (43), or were subjected to TUNEL assay (44). A diagram of histologic structure landmarks used for the analysis is illustrated in Fig. 3.

**Quantitative histologic analysis**

All data were analyzed in a double-blind fashion using coded specimens. Sections from different specimens were evaluated in a random sequence to...
FIGURE 5. Periodontal wound healing causes time-dependent changes in deep gingival connective tissue inflammatory cell recruitment (A), deep gingival connective tissue mononuclear inflammatory cell recruitment (B), osteoclast formation (C), and deep gingival connective tissue inflammatory cell apoptosis (D). All cell counts were quantified with the aid of an image analysis system. Inflammatory cells are reported as number of inflammatory cells per mm² of connective tissue on H&E-stained sections in the box area, as described in Materials and Methods. Osteoclasts were counted on TRAP-stained sections. The data are reported as number of osteoclasts per millimeter length of bone. Inflammatory cell apoptosis was quantified on TUNEL-stained sections. Nuclei of the positive cells were stained dark blue. The data are presented as percentage of apoptotic cells in deep gingival connective tissue. Peak number of inflammatory cells in deep gingival connective tissue was observed at day 3, along with a peak in inflammatory cell apoptosis. Thereafter, a time-dependent decrease in the number of inflammatory cells was observed. The number of mononuclear inflammatory cells in deep gingival connective tissue was elevated at day 0, and time-dependent decrease of this parameter was observed. Note the elevated number of osteoclasts at day 14.
prevent bias. Two independent examiners performed the analysis of the tissue sections. The interexaminer and intraexaminer variations were <10%. All measurements were performed with the help of computer-assisted image analysis using ImageProPlus software (Media Cybernetics, Silver Spring, MD). Images were captured, coded, stored on disk, and analyzed randomly at a later time. Both of the observers used the same sets of coded images to perform analysis. The number of apoptotic cells was measured in situ by the TUNEL assay using a TdT-blue label detection kit (Trivegen, Gaithersburg, MD). Nuclei were counterstained with Fast Red. Measurements from two tissue sections were averaged to provide values for each tooth block. These measurements included bone resorption, extent of the apical migration of the epithelium (epithelial downgrowth), and new cementum formation, as depicted in Fig. 3. Bone resorption was determined by quantifying the distance between CRJ and the coronal level of alveolar crest. Epithelial downgrowth was determined by measuring the distance between CRJ and the apical extent of the junctional epithelium. New cementum formation was determined by quantifying new cementum above notch. 

Inflammatory cells, osteoclasts, and inflammatory cell apoptosis

The same sections used in linear measurements were analyzed for inflammatory cell numbers. Images were captured at ×400 magnification. An area of interest was defined as a 1-mm² box in deep gingival connective tissue in close proximity to bone on the palatal side of each tooth. Based on our experience, this area is critical for the destructive and repair processes of the tooth-supporting apparatus in periodontal wound healing, as it is the location in which cellular changes are mostly expected. The apical boundary was set at the level of the notch, and the coronal boundary 1 mm above notch. The lateral boundary was set 1 mm away from the palatal root on one side and extended 1 mm palatal into the gingival space. All cell analyses were performed in this box drawn in all specimens. Specimens with unidentifiable landmarks were not analyzed. Based on a fixed and reproducible landmark (notch), such cell analysis provided means to examine temporal changes occurring in the same tissue area on all the sections. A minimum of five fields (i.e., upper left corner, upper right corner, lower left corner, lower right corner, and center) from each area of interest was quantified. Inflammatory cells included mononuclear and polymorphonuclear leukocytes. Mononuclear leukocytes included lymphocytes, macrophages, monocytes, or plasma cells. Polymorphonuclear leukocytes were identified by their multilobed nucleus. Inflammatory cell numbers were determined by measuring inflammatory cell numbers per mm² connective tissue.

Osteoclasts were detected using TRAP (43) approach and recognized as positive staining on large multinucleated cells directly lining the bone surface in Howship’s lacunae. Osteoclast numbers were determined by quantifying number of osteoclasts per mm of bone surface.

Inflammatory cell apoptosis was detected by the TUNEL technique (44) using a TdT-blue label detection kit, performed according to the manufacturer’s recommendations. The data are presented as number of apoptotic cells per 100 inflammatory cells.

Statistical analysis

For each parameter, groups injected with vehicle alone were compared with those injected with soluble receptors at each indicated time point using Student’s t test with SPSS software (SPSS, Chicago, IL). Statistical significance was defined as p < 0.05.

Results

Wound-healing pattern in untreated groups

The wound-healing parameters (epithelial downgrowth, bone resorption, and new cementum formation), deep gingival tissue inflammatory cell recruitment, number of osteoclasts, and inflammatory cell apoptosis were examined at days 0, 3, 14, and 35. It should be noted that the larger the value of the epithelial attachment, the worse the outcome of periodontal wound healing, because by migrating on the root surface the epithelium prevents the connective tissue from newly attaching on the root surface. As shown in Fig. 4 A, epithelial attachment did not improve considerably during healing. There was no obvious bone resorption observed at days 0 and 3, consistent with virtually no osteoclast at days 0 and 3. Bone resorption peaked at day 14, consistent with an elevated number of osteoclasts observed at the same time point. The net bone resorption was found improved at day 35 (Fig. 4B), consistent with fewer osteoclast numbers at the same time point (Fig. 5C). New cementum formation was observed as early as day 14 and peaked at day 35 (Fig. 4C). Given that before the periodontal treatment all animals were left to accumulate microorganisms to develop periodontal disease, the number of inflammatory...
cells in deep gingival connective tissue evaluated at day 0 was relatively high (Fig. 5A), consistent with a chronic inflammation typically found in periodontitis with low inflammatory cell apoptosis at day 0. Peak number of inflammatory cells in the same compartment was observed at day 3, consistent with an acute inflammation observed after the inception of wound healing. Elevated inflammatory cell apoptosis was observed at this time point (Fig. 5D). Thereafter, a time-dependent decrease in the number of inflammatory cells was observed (Fig. 5A). The number of mononuclear inflammatory cells in deep gingival connective tissue was
epithelial attachment, positive value represents decrease of epithelial downgrowth (improvement in wound healing outcome), while negative value represents increase of epithelial downgrowth (deterioration of wound-healing outcome). For bone height, positive value represents bone formation, while negative value represents bone resorption. For cementum formation, positive value represents cementum deposition. Fourteen days after surgery, the epithelial attachment was found 1.11 mm shorter in the group injected with soluble receptors compared with the untreated group \( (p < 0.05) \) (Fig. 6A). Moreover, bone height was \( \approx 1 \) mm greater in the treated group compared with the untreated group at day 14 \( (p < 0.05) \) (Fig. 6B). Consistent with this finding, a 90% reduction of osteoclast numbers in animals that received local injection of IL-1 and TNF soluble receptors compared with the untreated animals \( (p < 0.05) \) (Fig. 7C). Finally, more new cementum formation was observed in the treated group compared with the untreated group, but here the difference was not statistically significant \( (p < 0.05) \) (Fig. 6C).

**Histologic changes in healing tissues 35 days after surgery**

Although the group treated with soluble IL-1/TNF receptors clearly exhibited better healing at day 14, this benefit was entirely lost by day 35. At this time point, epithelial attachment was found 1.10 mm longer in the treated group compared with the placebo-treated group \( (p < 0.05) \) (Fig. 6A). Moreover, bone height was 0.47 mm lesser in the treated group compared with the untreated group \( (p < 0.05) \) (Fig. 6B). Consistent with this finding, the osteoclast numbers were greater in animals that received IL-1 and TNF soluble receptors compared with untreated animals, but the difference was not statistically significant \( (p < 0.05) \) (Fig. 7C). Finally, a 98% decrease in new cementum formation was observed in the group treated with IL-1 and TNF soluble receptors when compared with the group treated with vehicle alone \( (p < 0.05) \) (Fig. 6C).

**Deep gingival connective tissue inflammation**

Three days after surgery, the animals that had been treated briefly with soluble receptors had similar numbers of inflammatory cells in deep gingival connective tissue compared with the untreated animals. Fourteen days after surgery, a 47% reduction in inflammatory cells was observed in the group injected with soluble receptors compared with the untreated group \( (p < 0.05) \). This reduction was observed mostly in the mononuclear cell segment \( (Fig. 7, A \) and \( B) \). However, 35 days after surgery, there was a striking increase in inflammatory cell counts in deep gingival connective tissue in the treated group, whereas treated animals exhibited 2.65-fold increased inflammatory cells compared with untreated animals \( (p < 0.05) \) at the same time point. This shift in inflammatory cell recruitment resulted mostly from mononuclear cells \( (Fig. 7, A \) and \( B) \). Comparison of polymorphonuclear cells from treated and untreated animals in each time group reflected similar change as seen for mononuclear cells, but here the differences were not statistically significant (data not shown). Fig. 8 depicts representative histologic sections used for the analysis.

**Inflammatory cell apoptosis**

The number of apoptotic inflammatory cells in deep gingival connective tissue is shown in Fig. 7D. Representative histologic sections from these animals are shown in Fig. 9. Three days after surgery, there was no discernible difference between treated and untreated animals in inflammatory cell apoptosis. Fourteen days after surgery, a 5.7-fold increase in inflammatory cell apoptosis

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**FIGURE 8.** Histologic pictures representative of the tissue sections used in the analysis. Baseline control animals showed inflammatory cell infiltrate in deep gingival tissue on H&E-stained sections \( (A \) and \( B) \), consistent with experimental periodontitis. Treatment with IL-1 and TNF antagonists reduced inflammatory cell infiltration in deep gingival tissue at day 14, but increased it at day 35 after surgery. At day 14, sections from animals receiving vehicle alone showed substantial increase in inflammatory cell infiltrate in deep gingival connective tissue on H&E-stained sections \( (C \) and \( D) \), while sections from animals receiving IL-1/TNF soluble receptors showed a reduced inflammatory cell infiltrate \( (E \) and \( F) \). This pattern was reversed at day 35, with treated animals \( (I \) and \( J) \) exhibiting greater inflammatory cell infiltrate than untreated animals \( (G \) and \( H) \) or earlier time point animals \( (A-H) \). **Insets** drawn on \( A, C, E, G, \) and \( I \) show the areas magnified in \( B, D, F, H, \) and \( J, \) respectively. \( B, \) bone; CT, connective tissue. Original magnification: \( A, C, E, G, \) and \( I, \times 100; B, D, F, H, \) and \( J, \times 400. \)
was observed in the group injected with soluble receptors compared with the untreated group (p < 0.05) (Figs. 7D and 9). Thirty-five days after surgery, inflammatory cell apoptosis was observed to be 38% less in the group injected with soluble receptors compared with the untreated group (Figs. 7D and 9).

**Discussion**

In this study, a nonhuman primate model was used to assess the effect of jointly inhibiting IL-1 and TNF on the periodontal wound-healing process. Our study demonstrates that short-term application (14 days) of inhibitors of IL-1/TNF activity led to a significant improvement of periodontal wound healing, while longer-term (35 days) application of these agents had deleterious effects on the wound-healing outcomes.

In some human clinical trials, IL-1 or TNF antagonists alone do not appear to be as efficacious as expected, based on findings from animal studies. One potential explanation for this is that IL-1 and TNF are strongly synergistic (45–47). Therefore, we have used a combination of TNF and IL-1 inhibitors in an attempt to interfere with both cytokines and to reduce their potential redundancies of activity. We have previously reported that in a nonhuman primate model, the use of soluble receptors for IL-1 and TNF prevented the spread of inflammation, which in turn reduced loss of connective tissue and alveolar bone (10, 29, 39, 48). Others have shown that inhibiting both IL-1 and TNF results in a synergistic down-regulation of inflammation and bone loss in the context of rheumatoid arthritis (49). Furthermore, the utility of administering both IL-1 and TNF antagonists has been demonstrated for protection against endotoxemia (50).

Three major therapeutic approaches have been investigated to interfere with the proinflammatory effects of IL-1 or TNF. Neutralizing Abs to IL-1/TNF were found to be beneficial in diseases associated with excessive IL-1/TNF production (51, 52). Clinical trials with mAb against TNF-α that focused on rheumatoid arthritis and Crohn’s disease have demonstrated promising results (53). Second, administration of IL-1 receptor antagonist, the natural antagonist to IL-1, was shown to improve recovery after traumatic injury (25, 54). Third, exogenous soluble receptors to IL-1/TNF can bind to IL-1 and TNF to prevent IL-1/TNF from binding to their receptors on host cells.

These results suggest that IL-1 and TNF have a detrimental effect in the early phase of periodontal wound healing, while they may be beneficial in the long-term. Furthermore, short-term limitation of their effects in vivo allows for an improvement of wound-healing parameter, while long-term application worsens wound healing. This interpretation is consistent with the findings that overproduction of IL-1 and TNF has been demonstrated in periodontal disease etiologies (55). Soluble receptors to IL-1/TNF similar to those used in this study have been shown to significantly reduce tissue destruction and inflammation in experimental periodontitis (10, 29, 39, 48). TNF and IL-1 were shown to sustain, amplify, and prolong inflammation and tissue destruction. This is achieved through activating inflammatory cells to release cytokines such as IL-1 and TNF, and small molecule mediators such as NO (56). In our study, interfering with IL-1 and TNF activity resulted in a significant improvement of periodontal healing outcomes in the animals treated for 14 days with soluble receptors compared with untreated animals.

However, by day 35, this benefit was entirely lost. As shown in Fig. 7, inflammatory cell infiltration in deep gingival connective tissue was significantly greater in the animals treated with soluble receptors than in the untreated animals observed 35 days after surgery. Also at day 35, inflammatory cell apoptosis in deep gingival connective tissue was reduced in animals treated with soluble receptors. These results suggest that IL-1/TNF might have a role in resolving inflammation at a later stage of wound healing. This interpretation is consistent with recent reports that demonstrated that mice could not resolve late-phase inflammation if they were deficient in TNF (57). Also, treatment with anti-TNF-α mAbs was shown to compromise inflammatory cell clearance in the lungs of wild-type mice after infection with *Rhodococcus equi* (58). Nathan (9) showed that TNF was involved in the late phase of wound healing, in switching from the tissue-damaging mode to the tissue repair-promoting mode after debris and dead cells were no longer present. Another explanation is that IL-1 might play an essential role in antibacterial defense in a challenging environment in which microflora are deleterious to the wound-healing process (17). As a result, the early improvement of periodontal healing has been lost in animals treated long-term with IL-1 and TNF soluble receptors compared with the untreated animals. It is unlikely that long-term injection of IL-1/TNF soluble receptors would stimulate animals to generate Ab and thus obviate the benefits of the inhibitors observed at 14 days (59). The relatively short time frame of this experiment relative to Ab generation rules out this possibility particularly in light of our previous study showing that soluble receptors to IL-1/TNF were still able to reduce inflammatory responses even at the end of a longer study (6 wk) (39). In another published study, etanercept (TNF antagonist) were still very effective at reducing peri-implant lesions of spontaneously occurring active endometriosis in the baboon after 8 wk (60).

TNF-α and IL-1α are capable of inducing osteoclastogenesis (61). As anticipated, short-term applications of the cytokine inhibitors did reduce postsurgical osteoclastogenesis when compared with untreated animals, although longer-term applications showed a trend in the opposite direction, toward increased numbers of osteoclasts in the inhibitor-treated animals. This increase in osteoclasts at day 35 seemed to parallel the increase in mononuclear cell infiltration observed at the same time point, consistent with the

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**FIGURE 9.** Representative histologic sections illustrating that treatment with IL-1 and TNF antagonists increased inflammatory cell apoptosis in deep gingival connective tissue on periodontal wound healing at day 14 after surgery. TUNEL-stained sections are shown from treated (A) and untreated animals (B). Original magnification: ×400.
observation that mononuclear cell products stimulate osteoclastogenesis (62). The resurgence of the inflammatory cell infiltration and the deterioration of wound-healing outcomes observed in animals treated for a long-term with the cytokine inhibitors did not appear to be a result of increased bacterial growth, as all the strains tested from oral cultures remained unchanged between treated vs untreated animals (data not shown).

Multiple time points are necessary for studying the periodontal wound-healing process, due to the complexity and dynamic nature of this process. In this study, to capture periodontal wound-healing events, we used three different time points that are important in wound-healing processes: day 3 for the peak of inflammation; day 14 for maximal formation of granulation tissue; and day 35 for tissue remodeling (2). Our data indicate a series of effects of the soluble receptors over the course of periodontal wound healing: within 14 days after the wound was incurred, the inhibition of proinflammatory cytokines was beneficial overall in our model. However, prolonged application of these inhibitors appears not to favor the healing process, rather to be detrimental to the overall outcome. This study supports the concept that modulation of inflammatory process through interfering with IL-1/TNF activity can be potentially beneficial to improve periodontal wound healing if it is used only for a short time, while longer-term usage may not be appropriate, particularly in a challenging environment with a high prevalence of oral pathogens.

References

8. Beutler, B., and A. Cerami. 1986. Cachectin and tumor necrosis factor as two inflammatory cytokines was beneficial overall in our model. However, prolonged application of these inhibitors appears not to favor the healing process, rather to be detrimental to the overall outcome. This study supports the concept that modulation of inflammatory process through interfering with IL-1/TNF activity can be potentially beneficial to improve periodontal wound healing if it is used only for a short time, while longer-term usage may not be appropriate, particularly in a challenging environment with a high prevalence of oral pathogens.

References


