ORTHODONTICS & CRANIOFACIAL RESEARCH

ORIGINAL ARTICLE

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Dates:
Accepted 20 March 2010

To cite this article:
Santos RL, de Farias MLF, de Mendonça LMC, Gonçalves RT, Martins MA, de Souza MMG: Effects of immunosuppressant FK-506 on tooth movement
Orthod Craniofac Res 2010;**13**:153–161

Effects of immunosuppressant FK-506 on tooth movement

Structured Abstract

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Objective – To test the hypothesis that immunosuppressant tacrolimus treatment can interfere with bone turnover and rate of tooth movement.

Material and Methods – One-hundred twenty Wistar male rats were divided into four groups: Group 1 (rats subjected to orthodontic movement plus treatment with saline solution vehicle), Group 2 (rats subjected to orthodontic movement plus treatment with FK506), Group 3 (rats treated with FK506 only), and Group 4 (rats treated with saline solution vehicle). The maxillary incisors were laterally moved with a reciprocal load of 35 cN. The dosage of FK506 was 2 mg/kg/day. Howship's lacunae, osteoclasts, and macrophages were counted.

Results – Tooth movement was found to be greater in Group 1 than in Group 2 for all time periods (on days 3, 7, and 14), although a significant difference was observed only on days 7 and 14 ($p < 0.05$). The number of osteoclasts was smaller in Group 1 than in Group 2, whereas the number of Howship's lacunae was greater.

Conclusion – FK506 has the capacity of promoting osteoclasts inhibition with probable osteoclastic apoptosis of alveolar bone following tooth movement.

Key words: bone; immunosuppressant; orthodontics; tooth movement

Introduction

Tacrolimus (FK506) is an immunosuppressive agent derived from *Streptomyces tsukubaensis* (1), being widely used in patients submitted to organ transplantation (2). Some authors (3, 4) have suggested that FK506 exerts its anti-inflammatory effect mainly by interfering with the activation of T cells, suppressing the production of cytokines, particularly TNF-α, IL-1β, IL-2, and IL6, modulating the inflammation, and decreasing both tissue destruction and bone resorption. On the other hand, bone turnover and development of severe osteoporosis have been reported (5).

Studies using cell culture (6, 7) have demonstrated that not only messenger RNAs of NFATc1, NFATc2 and NFATc3, essential transcription factors for osteoclastic differentiation are present in the osteoclast-precursor cells, but also that FK506 inhibits the final phases of cell life cycle through osteoclastic apoptosis. As a whole, these findings are in accordance with the idea that the mechanisms by which osteoclastogenesis is

inhibited and osteoclastic apoptosis is promoted are similar to those involved for inhibiting the production of transcription factor NFAT and inflammatory cytokines within T lymphocytes (8). Therefore, the objective of the present study was to test the hypothesis that FK506 treatment can interfere with bone turnover and the rate of tooth movement.

Materials and methods

Animal model

A total of 120 Wistar male rats (*Rattus norvegicus*) aged 9 weeks and weighting 280–300 g were housed according to the guidelines for animal research as recommended by the Fundação Osvaldo Cruz of Rio de Janeiro (FIOCRUZ-RJ). The immunosuppressive agent FK506 (Tacrolimus, PROGRAF®, Astellas, Ireland) was orally administrated at a dose of 2 mg/kg/day in form of suspension containing water and 5% dextrose (9). The treatment was initiated 14 days before the appliance installation and kept until the end of the experimental periods. The animal experiment was approved by the ethics committee on animal research of the Federal University of Rio de Janeiro (UFRJ).

Experimental groups

The rats were randomly divided into four groups consisting of 30 animals each as follows: Group 1, consisting of rats subjected to orthodontic movement plus treatment with saline solution vehicle; Group 2, consisting of rats subjected to orthodontic movement plus treatment with FK506; Group 3, consisting of rats treated with FK506 only; and Group 4, consisting of rats treated with saline solution vehicle. Animals were killed at days 0, 3, 7 and 14 after placement of the orthodontic appliance.

Appliance design

The appliance was made according to description made by Arias and Marquez-Orozco (10) regarding wire diameter and installation (Fig. 1A). The initial load of 35 gf (10) to be exerted by the orthodontic appliance was determined before its insertion by means of a ball dynamometer (Dentaurum 040-711; Ispringen, Germany). The rats were anesthetised with intraperitoneal injection of sodium thiopental 50 mg/kg (Cristália, Campinas, SP, Brazil). Incisor gaps were measured from the cervical region of the tooth and recorded by two investigators using a 0.01-mm precision calliper (Starret, Itú, SP, Brazil), and the mean values were recorded when the animals were killed.

Weight assessment

FK506 causes metabolic and gastrointestinal alterations (11, 12), and this factor can interfere with the weight gain in the animals. The presence of orthodontic appliance can also interfere with weight gain by making normal alimentation difficult. Therefore, the animal's weight was measured every day in order to adjust the dosage of FK506 to be administered and to verify the influence of both immunosuppressor and appliance on the weight gain.

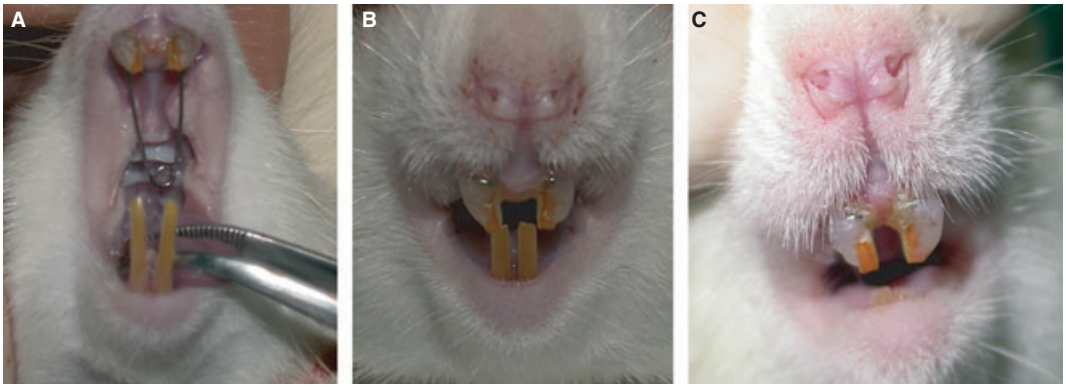

Fig. 1. (A) Photograph of Appliance made according to description from Arias and Marquez-Orozco (10). (B–C) Photograph showing upper incisors (frontal view) of rats treated with saline solution vehicle (B) and rats orally treated with FK506 (2 mg/kg/day) (C) following 14 days of orthodontic movement.

Blood count

Total and differential (lymphocytes, monocytes, eosinophils and neutrophils) leucocyte counts were evaluated on day 0 (before appliance installation) and on sacrifice days in all groups in order to monitor the immunosuppressive effect of tacrolimus. Blood was collected from the tail tip of each rat. Leucocyte count was performed by means of a light microscope (Olympus BX40; Olympus, Hamburg, Germany).

Histological procedure

After 3, 7 and 14 days of orthodontic movement, 10 rats in each subgroup were killed and then decapitated. Their heads were dissected and the pre-maxillas were removed and stored in 10% formaldehyde solution for 24 h. After that period of time, the samples were washed with phosphate-buffered saline (PBS) solution. The samples were decalcified with 10% EDTA solution for 45 days at room temperature, then gradually dehydrated through ethanol series and embedded in paraffin. The pieces were frontally sectioned at the foramen region, yielding transversal sections of 4 mm thick that were stained with haematoxylin and eosin so that the number of Howship's lacunae could be evaluated. Immunohistochemistry using monoclonal antibodies ED1 was employed to evaluate the number of macrophages and osteoclasts. Cells were considered osteoclasts when they were multinucleated, ED1 positive ($ED1^+$), and located within the bone or at the osseous surface (13). The baseline (day 0) numbers of Howship's lacunae, osteoclasts and macrophages were counted immediately before the beginning of FK506 treatment (pre-experimental period).

The histological study focused on the alveolar bone located laterally in relation to the incisors, which were divided into pressure (distal face) and traction (mesial face) sides according to the cervical-apical root axis. Twenty sections were randomly selected for counting.

One operator, who was blinded to the treatment objectives, recorded the data from the sections by using a light microscope (Olympus BX40) with 100 times magnification. An area of 10 mm^2 was examined for counting the number of osteoclasts, macrophages, and Howship's lacunae. In order to confirm the information gathered, microphotographs of periodontal ligament on the pressure side were taken (60 × magnification) by using a device (Image-Pro®, Media Cybernetics, Silver Spring, Maryland, USA) mounted onto the light microscope (Olympus BX 40).

Immunohistochemical evaluation

Both macrophages and osteoclasts were identified through immunohistochemistry with ED1, a monoclonal antibody that recognizes cytoplasmatic antigen within monocytes, macrophages and osteoclasts of rats (13, 14). The tissue-specific pattern of ED1 for bones is the same of tartrate resistant acid phosphatase (TRAP), which is frequently used to identify osteoclasts (15, 16).

Initially, consecutive sections were selected and then deparaffinized and rehydrated. The sections were treated with 5% borax for load inhibition and then washed with PBS for 10 min. Next, enzymatic treatment was required for antigenic recovery. After washing in PBS, the sections were treated with 6% H_2O_2 in methanol for 20 min and then washed in PBS. The sections were incubated with 5% PBS/BSA (Sigma, St Louis, MO, USA). After pre-incubation, the sections were incubated with mouse monoclonal anti-rat antibody ED1 (1:100) (Serotec, Raleigh, NC, USA) overnight. After washing in PBS-Tween (0.25%), the sections were incubated with the labelled streptavidin-biotin kit (LSAB™, Dako, Carpinteria, CA, USA) for 1 h within moist chamber. Then, the sections were treated with 3,3′-diaminobenzidine tetrahydrochloride (Dako, Carpinteria, CA, USA) for 10 min and used as chromogen. Diluted solution of Harris haematoxylin was used as counterstain. Primary antibody was replaced with PBS for negative immunohistochemical control.

The data were evaluated by analysis of variance (ANOVA), and Newman-Keuls multiple comparison test was used to determine any statistically significant difference between the experimental groups ($p < 0.05$).

Densitometric analysis

With regard to densitometry, the animals were analysed on day 0 (14 days before appliance installation – pre-experimental period) and on days 3, 7 and 14 after being killed. The bone mineral content was measured and then divided by the area so that the bone mineral density of the right femur of each rat could be obtained through dual-energy X-ray absorptionmetry (Prodigy, GE/LUNAR, USA). The femur was put into a vessel of

equal size and rice grains were poured into it so that the bone was completely covered, thus simulating the surrounding soft tissues. Bone scan and data analysis were carried out by using specific software for small animals that could be manually adjusted for analysis of the region of interest. The resolution (in pixels) was 0.3×0.6 mm for a collimator of 0.84 mm in diameter. The scanned area was 9.9 mm in width and 11.8 mm in length. The scan time for the femur was 0.5 min. The total area of the femur was selected for evaluation of bone density.

Results

Tooth movement

Before placement of the appliances, there was no measurable space between the upper incisors. Group 1 showed greater tooth movement (Fig. 1B) compared to Group 2 (Fig. 1C) on days 3, 7 and 14 (Fig. 2); however, a significant difference ($p < 0.05$) was observed only on days 7 and 14, respectively, (2.09 + 0.10 and 1.66 + 0.09 mm) and (3.06 + 0.05 and 2.48 + 0.11 mm).

Effect of appliance placement and FK506 treatment on weight gain

The orthodontic appliance was well tolerated by the animals during the experimental period and caused no soft tissue irritation. The weight gain regarding each period of time was calculated on the basis of the initial treatment with FK506. Both immunosuppressant and appliance were found to have influence on the weight gain, because the non-treated animals had the highest gains. Group 3 had highest weight gain (41.0 + 1.2 g) compared to Group 1 (35.3 + 2.0 g) after 28 days (pre-experimental period of 14 days plus experimental period of 14 days), but no significant difference was observed ($p > 0.05$). On the other hand, Group 2 had the lowest weight gains on days 3 (15.7 + 2.3 g), 7 (16.7 + 2.2 g), and 14 (21.4 + 1.6 g). Significant differences were observed between Group 2 and Groups 1 and 3 in all time periods of study (Fig. 3).

Effect of appliance placement and FK506 treatment on leucocyte count

Immunosuppression was observed in the animals from Group 2 and 3 as leucocytes and lymphocytes counts were shown to have similar and decreasing values during the experiment in all time periods. Also, statistically significant differences were observed between both groups and their respective controls (day 0 – leucocyte count before installing orthodontic appliance). There was a significant difference between Group 2 and Group 1 on days 7 and 14 ($p < 0.05$). Contrary to Groups 2 and 3, however, Group 1 (rats subjected to orthodontic movement plus treatment with saline solution) showed increasing values for leucocytes and lymphocytes counts, i.e., there was body's response to stimuli (force) applied to teeth. Group 1 also had a significant difference between 14th day and baseline (day 0) ($p < 0.05$).

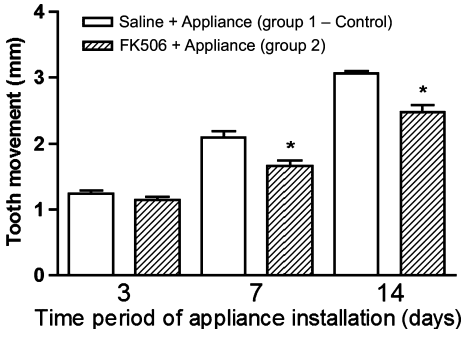

Fig. 2. Tooth movement of rats treated with FK506 (2 mg/kg/day) (shadowed column) or saline (open column) observed on days 3, 7 and 14 following appliance installation. The values represent mean ± standard deviation regarding 10 experimental animals. $^{*}p < 0.05$ compared to vehicle-treated animals.

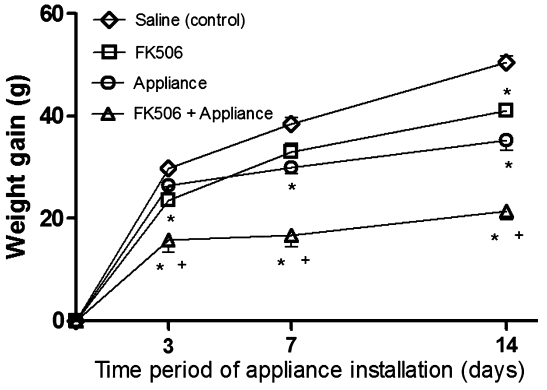

Fig. 3. Weight gain in Group 1 (rats subjected to orthodontic movement plus treatment with saline solution vehicle) (circle), Group 2 (rats subjected to orthodontic movement plus treatment with FK506) (triangle), Group 3 (rats treated with FK506 only) (square), and Group 4 (rats treated with saline solution vehicle) (lozenge) on days 3, 7 and 14 following installation of appliance. The values represent mean ± standard deviation regarding 10 experimental animals. $^{*}p < 0.05$ compared to non-treated animals; $^{+}p < 0.05$ compared to FK-506-treated animals.

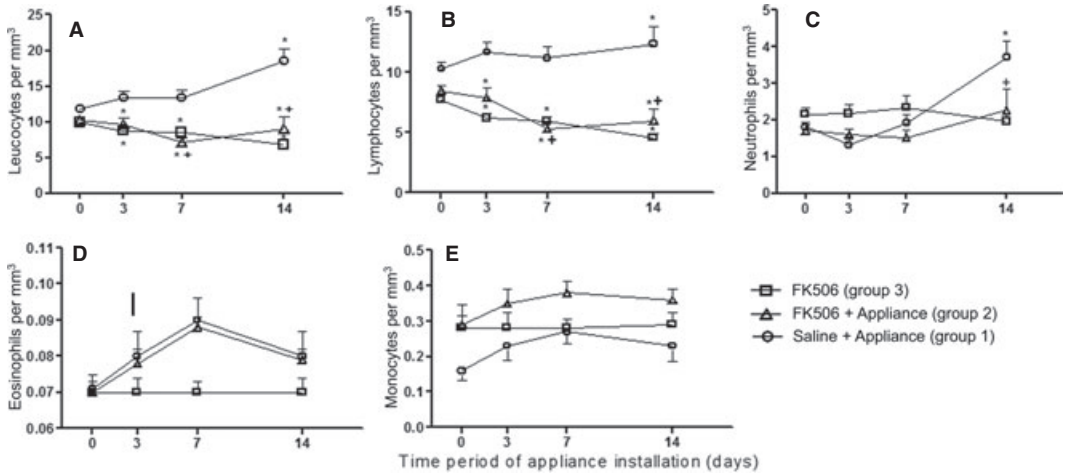

Fig. 4. Total leucocytes count (A), lymphocytes (B), neutrophils (C), eosinophils (D), and monocytes (E) in Group 1 (rats subjected to orthodontic movement plus treatment with saline solution vehicle) (circle), Group 2 (rats subjected to orthodontic movement plus treatment with FK506) (triangle), Group 3 (rats treated with FK506 only) (square) on days 3, 7 and 14 following installation of appliance. The values represent mean ± standard deviation regarding 10 experimental animals. $^{*}p < 0.05$ compared to respective controls; $^{+}p < 0.05$ compared to orthodontically treated animals.

In Groups 2 and 3, the numbers of neutrophils were found to be similar and no significant difference was observed ($p > 0.05$). Group 1 showed an increased neutrophils count on day 14, which was significantly different compared to the respective control (day 0) ($p < 0.05$).

Eosinophils and monocyte counts showed similar patterns between Groups 1 and 2, with increased values on day 7 and decreased values on day 14. Group 3 had an increased monocyte count compared to Group 1 for day 0, which was kept for other time periods. No significant difference regarding this kind of cells was observed between the groups in all periods of time studied ($p > 0.05$) (Fig. 4). One can observe a trend of increase in the number of eosinophils because of the presence of orthodontic appliance, whereas the presence of FK506 promotes an increase in the number of monocytes.

Osteoclast and Howship's lacunae counts

In Group 3, osteoclast count ($ED1^{+}$) (Fig. 5) showed evidence for the influence of FK506 on bone metabolism, which was found to be similarly increased in all time periods. Also, there was significant difference in relation to the day 0 (Osteoclast count before installing orthodontic appliance) ($p < 0.05$). In Group 1, the number of osteoclasts was found to be increased on days 3 and 7, although there was a decrease on day 14, thus indicating reorganization of the periodontal ligament (tissue homeostasis). In addition, there was a significant difference in relation to day 7 ($p < 0.05$). Interestingly, the same pattern was observed in Group 2 despite presenting higher values, with significant difference in all time periods ($p < 0.05$) (Fig. 6).

Howship's lacunae count was found to be similar to the osteoclast count. The numbers of lacunae observed on days 3 and 7, respectively, in Group 3 (2.26 ± 0.26 lacunae/10 and 2.33 ± 0.28 lacunae/10 mm^2) and Group 2 (2.36 ± 0.26 lacunae/10 and 2.46 ± 0.30 lacunae/10 mm^2) were smaller than those observed in Group 1 (2.50 ± 0.28 lacunae/10 and 2.9 ± 0.27 lacunae/10 mm^2) (Fig. 7). This means that osteoclastic activity was greater in Group 1 than in Groups 2 and 3. There were significant differences in Groups 1, 2, and 3 for all time periods of evaluation in relation to respective controls (day 0 – Howship's lacunae count before installing orthodontic appliance) ($p < 0.05$), except Group 1 on day 14 because of decreased bone resorption and reorganization of periodontal tissue ($p > 0.05$) (Fig. 7).

Macrophages count

Macrophage count (Fig. 5) was found to be significantly increased in all time periods of evaluation, with significant difference in relation to respective control (day 0) ($p < 0.05$). Group 2 had the highest values on

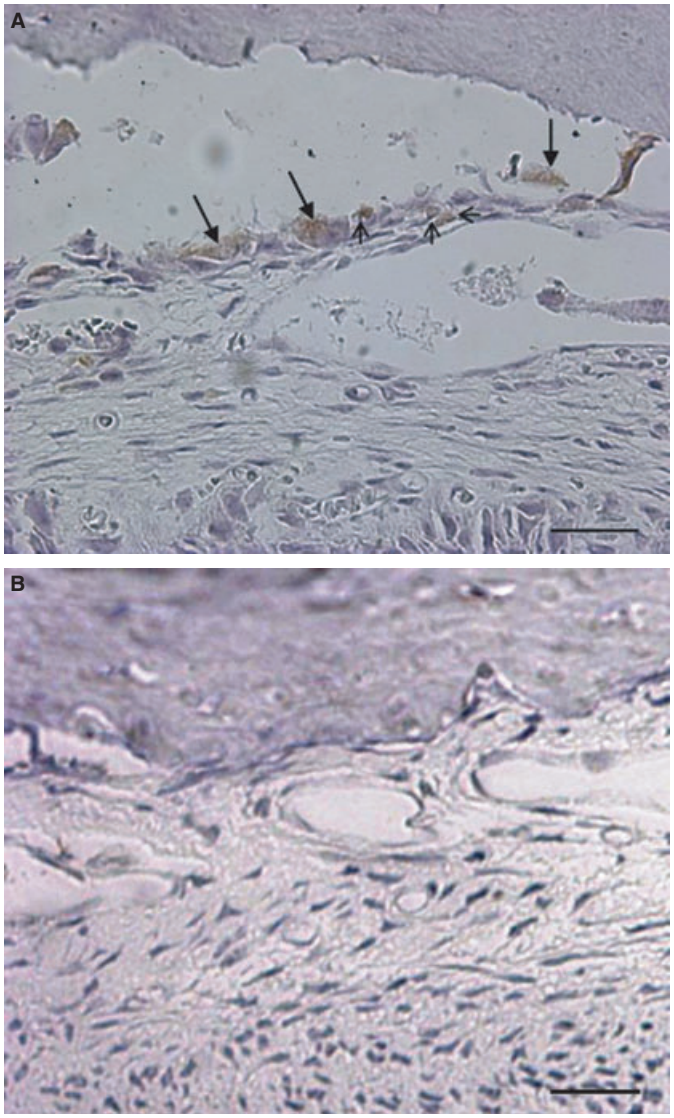

Fig. 5. Microphotographs of histological sections using immunohistochemistry (ED1$^+$) for osteoclasts (giant multinucleated cells located within bone or at bone surface) (long arrows) and macrophages (mononucleated cells out of blood vessels and within periodontal ligament) (short arrows) at the pression side in animals treated with only FK506 on day 7 following appliance installation (A). (B) Negative control. The cells were counted by using a schematic diagram with a 10-mm^2 area (1000 × magnification; scale:100 μm).

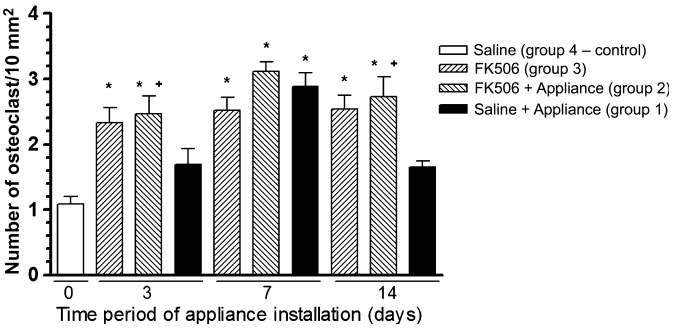

Fig. 6. Osteoclast counts from histological sections subjected to immunohistochemistry (ED1$^+$ for multinucleated cells located within bone or at osseous surface) for Group 1 (rats subjected to orthodontic movement plus treatment with saline solution vehicle) (closed column), Group 2 (rats subjected to orthodontic movement plus treatment with FK506) (descending stripped column), Group 3 (rats treated with FK506 only) (ascending stripped column), and Group 4 (rats treated with saline solution) (open column) on days 3, 7, and 14 following installation of appliance. The values represent mean ± standard deviation regarding 10 experimental animals. *$p < 0.05$ compared to respective controls; $^+p < 0.05$ compared to orthodontically treated animals.

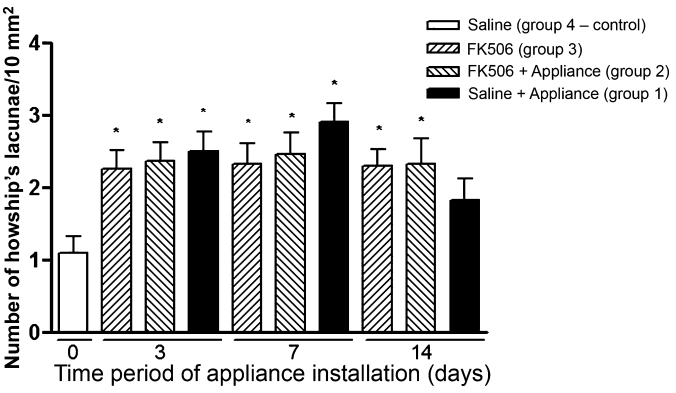

Fig. 7. Howship's lacunae counts from histological sections stained with HE for Group 1 (rats subjected to orthodontic movement plus treatment with saline solution vehicle) (closed column), Group 2 (rats subjected to orthodontic movement plus treatment with FK506) (descending stripped column), Group 3 (rats treated with FK506 only) (ascending stripped column), and Group 4 (rats treated with saline solution) (open column) on days 3, 7 and 14 following installation of appliance. The values represent mean ± standard deviation regarding 10 experimental animals. *$p < 0.05$ compared to respective controls.

day 3 (7.73 ± 0.43 macrophages/10 mm^2), day 7 (8.95 ± 0.20 macrophages/10 mm^2), and day 14 (8.39 ± 0.44 macrophages/10 mm^2) compared to non-treated group (1.87 ± 0.19 macrophages/10 mm^2) (Fig. 8). This represented an increase of seven cells for each point studied.

Bone densitometry

The bone densitometry showed decreasing values during the experiment; however, significant difference ($p < 0.05$) was observed on day 28 only in relation to respective control (day 0) (Table 1).

Apoptosis

It was observed indications of cellular apoptosis in the groups subjected to FK506 application (Groups 2 and 3). Osteoclasts presented morphological changes with presence of autophagic vacuoles, reduced cell size, increased eosinophilia, formation of apoptotic bodies and nucleus fragmentation (Fig. 9).

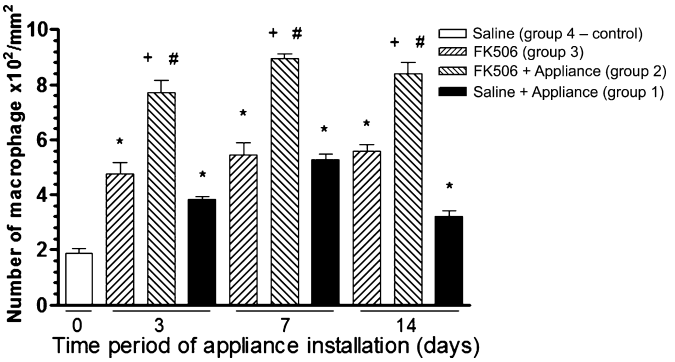

Fig. 8. Macrophage counts (ED1$^+$) obtained through histological sections of the periodontal ligament region of saline-treated rats (open column), rats subjected to orthodontic movement plus treatment with saline solution vehicle (closed column), rats subjected to orthodontic movement plus treatment with FK506 2 mg/kg/day (descending stripped column), and rats treated with FK506 2 mg/kg/day only (ascending stripped column) on days 3, 7, and 14. The values represent mean ± standard deviation regarding 10 experimental animals. $^*p < 0.05$ compared to respective controls; $^+p < 0.05$ compared to orthodontically treated animals. $^\#p < 0.05$ compared to FK506-treated animals.

Table 1. **Bone densitometry of right femurs of FK506-treated rats**

Time period	MBD (μg/cm^2)
Day 0	152.2 ± 1.8
Day 17	148.2 ± 3.8
Day 21	146.6 ± 4.4
Day 28	140.9 ± 5.1*

The values represent mean ± standard deviation regarding 10 experimental animals. $^*p < 0.05$ compared to vehicle-treated animals. The animals were evaluated on day 0 (14 days before appliance installation) and on days 3, 7 and 14 (killed). MBD = mean bone density.

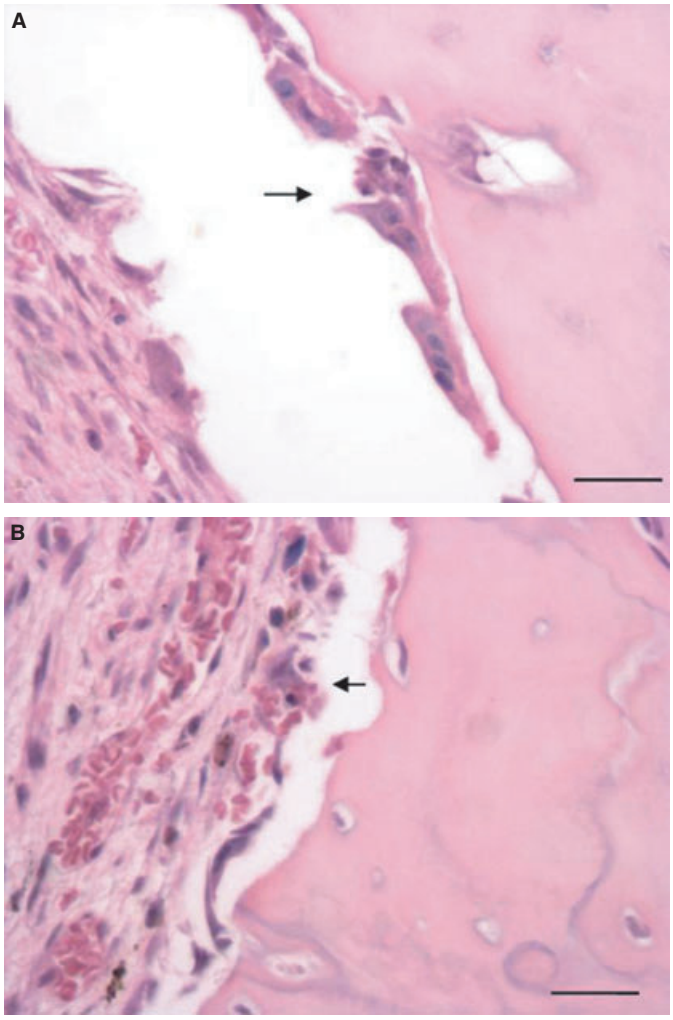

Fig. 9. Microphotographs of histological sections using Haematoxylin and Eosin. Osteoclastic apoptosis (arrows) at the pression side in animals subjected to orthodontic movement plus treatment with FK506 (A) and animals treated with FK506 only (B) following 7 days of appliance installation. (600 × magnification; scale: 100 μm).

Discussion

Previous studies have demonstrated that treatment with FK506 (tacrolimus) can induce bone loss in humans (17) as well as in animals (5, 18). In cell cultures, on the other hand, FK506 can also inhibit the final phases of life cycle of osteoclast-precursor cells through induction of apoptosis (6, 7). It has been suggested that FK506 inhibits production of pro-inflammatory cytokines, particularly TNG-α, IL-1β and IL-6 (3), both modulating the inflammation and decreasing tissue destruction and bone resorption (4). Because FK506 possesses the capacity to alter bone metabolism, one can suggest that it can interfere with the rate of tooth movement – the reason for the present study.

According to Reitan & Kvam (19), there are major differences between the teeth of rodents and humans. However, the rat incisor may be a useful model, because it can be moved by applied mechanical forces. Incisors quickly respond to orthodontic forces ranging from 20 to 40 gf (20). A load of 35 gf was used in the present study (10). It was observed that animals subjected to orthodontic treatment plus FK506 treatment (Group 2) had a smaller amount of tooth movement. The small number of Howship's lacunae seen in these animals may be because of the decreased osteoclastic activity (6, 7), although an increased number of osteoclasts (ED1$^+$) was observed as well – a finding also reported by Takayanagi et al.(7) and Hirotani et al.(6) following FK506 application. For Noxon et al.(21), the actual number of osteoclasts is determined by their level of recruitment and differentiation, probably modulated by apoptosis, and this finding is in accordance with recent works (6, 7) showing that FK506 can

inhibit the final phases of life cycle of these cells through induction of osteoclastic apoptosis.

Because the influence of FK506 on bone metabolism depends mainly on the dose administered (9), in the present experiment doses were daily calculated and adjusted according to the animal's weight gain. Some factors can interfere with weight gain, such as metabolic and gastro-intestinal changes (11, 12) caused by FK506. The presence of orthodontic appliance can also have an influence as it makes feeding more difficult, which might explain why animals receiving either orthodontic treatment or FK506 treatment had low weight gain compared to animals treated with saline solution (Group 4). In the present study, weight gain observed in FK506-treated animals was higher than that found by Sabry et al.(9) and Hayakawa et al.(22), who used the same daily FK506 dosage. In fact, the use of an orthodontic appliance in combination with FK506 treatment resulted in significant decrease in the weight gain, a joint influence of both factors.

With regard to bone densitometry, the femurs of these animals showed decreasing values of bone mineral density on day 28, thus supporting some findings from the literature (5, 17, 18). According to Cvetkovic et al.(5), FK506 application causes imbalance in bone activity (osteoblastic/osteoclastic) because of the significant increase in Parathyroid Hormone (PHT) levels, which was observed at a dosage higher than that used in the present study. On the other hand, Kirino et al.(23) have reported a significant increase in parathyroid hormone (PTH) with maximum peak on day 21 by using a lower dose, but an increased PTH resulting from continuous FK506 administration can lead to bone loss. Nevertheless, histological data demonstrated that FK506 can significantly reduce the induction of alveolar bone loss and granulocytes infiltration (4) because of its capacity to inhibit osteoclastogenesis '*in vivo*' and '*in vitro*'(7) by means of osteoclastic apoptosis. Such an effect would result in inactivation of NFATc1, NFATc2, and NFATc3 (messenger RNAs) existing within osteoclast-precursor cells (6).

Osteoclasts are the main cells involved in the process of alveolar bone remodelling and there seems to be a direct relationship between rate of tooth movement and number of osteoclasts (13). In the present study, however, the number of osteoclasts ($ED1^+$) observed in FK506-treated animals was very similar to that of animals subjected to orthodontic movement plus FK506 treatment and significantly greater compared to control animals (Group 4), a finding also corroborated by some authors (6, 7, 16, 23). In addition, this increase did not result in increased osteoclastic activity in the maxilla of animals being treated with FK506 and appliance.

Osteoclasts are cells deriving from the same linage of monocytes and macrophages (16). Some studies (24, 25) have shown evidence of macrophage presence next to tension area following the beginning of tooth movement. This suggests that these cells can play an important role in removing hyalinized tissues and remodelling them either directly or indirectly (16, 25), although they are more likely to be found in greater amount as the number of osteoclasts increases as well. The behaviour of macrophages during immunosuppressive therapy is a theme of great interest (26). Studies (27, 28) have reported that FK506 not only can inhibit apoptosis of macrophages and eosinophils (29) but also can increase the number of pro- and anti-apoptotic proteins in FK506-treated cells (27, 28). This might explain our findings showing increased number of macrophages observed in the region of periodontal ligament following FK506-treatment in addition to a trend towards an increase in monocytes. This greater number of macrophages could also be influenced by the long period of compression of the periodontal tissue and existence of hyalinization areas (30).

Conclusion

The hypothesis that treatment with FK506 interferes with bone turnover and rate of tooth movement was demonstrated. However, by observing the lower rate of tooth movement in animals subjected to orthodontic movement plus FK506 treatment, the number of osteoclasts and macrophages was found to be increased despite the small number of Howship's lacunae. As a whole, these findings showed that FK506 has the capacity of promoting osteoclasts inhibition with probable osteoclastic apoptosis of alveolar bone next to the orthodontically moved teeth.

Clinical relevance

Tacrolimus (FK506) is an immunosuppressive agent being widely used in patients subjected to organ transplantation. FK506 exerts its anti-inflammatory

effect mainly by interfering with the activation of T cells, by suppressing the production of cytokines, particularly TNF-α, IL-1β, IL-2, and IL-6, by modulating the inflammation and by decreasing both tissue turnover and bone resorption. As such it could interfere with orthodontic tooth movement. Therefore, knowledge of the influence exerted on bone and dental movement allows treatment to be safe and predictable.

Acknowledgement: We thank the Rio de Janeiro State Research Supporting Foundation (FAPERJ) for the research funding and the Department of Pathological Anatomy of the Federal University of Rio de Janeiro for the great help in carrying out this research.

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