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The Effect of Platform Switching on Periimplant Crevicular Fluid Content During Early Wound Healing

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Abstract

Purpose—The objective of this study was to investigate the soft tissue response and periimplant crevicular fluid (PICF) content around platform-switched (PS) and platform-matched (PM) implants during early healing.

Materials and Methods—Non-smokers treatment planned to receive a single implant in 2 quadrants were recruited. Two-stage implant placement protocol with 1 PM and 1 PS implant was implemented. Periimplant probing depths (PDs), modified sulcus bleeding index, and plaque indices were recorded, and PICF was collected at 1, 2, 4, and 6 weeks after abutment connection.

Results—PD readings were higher at week 1 than at week 6 for both groups ($P = 0.0005$). PD was statistically deeper in PM than in PS at week 1 ($P = 0.03$). There was a time-dependent decrease in total PICF volume for both groups. This decrease was statistically significant for PS ($P = 0.0005$), with no differences between the 2 groups at any time ($P > 0.05$). The decrease observed in both PM and PS for PICF interleukin 6 and macrophage inflammatory protein-1 β , and in PS for

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Approval

The clinical study was approved by the Institutional Review Board of The Ohio State University (protocol no. 2011H0355).

Disclosure

The authors claim to have no financial interest, either directly or indirectly, in the products or information listed in the article. The study was supported by the authors' own institutions.

tumor necrosis factor- α (TNF- α) was statistically significant ($P = 0.03$). TNF- α was statistically higher in PS than in PM at week 1 ($P = 0.005$).

Conclusion—Within the limits of this study, it seems that periimplant soft tissue response around PM and PS implants is mostly similar during the early healing period.

Keywords

dental implant; abutment; cytokines; gingival crevicular fluid

Periimplant marginal tissue health has been accepted as one of the main criteria to assess the long-term success of dental implants.¹ A successful dental implant might have a radiographic marginal bone loss of 1.5 to 2.0 mm during the first year of loading because of bone remodeling.^{1–4} The periimplant bone remodeling is initiated immediately after the exposure of the implant to the oral environment regardless of a submerged or nonsubmerged surgical approach.⁵

“Platform switching” is an innovative concept in which diameter mismatch is created between implant fixture and the abutment.⁴ Since the discovery of platform switching, several theories have been developed to explain how this protocol may prevent periimplant marginal bone loss.^{4,6–8} A biomechanical analysis using 3-dimensional finite element models suggested that the platform-switched (PS) configuration has the biomechanical advantage of shifting the stress concentration away from the cervical bone-implant surface, whereas it also has the disadvantage of increasing stress in the abutment or abutment screw.⁹ The biologic theory assumes that shifting the implant-abutment junction may medialize the location of the biologic width.⁴ Canullo et al¹⁰ focused on the role of micro-organisms and explored the relationship between bacterial biofilms and switched microgap location; nevertheless, they reported similar bacterial growth between PS and platform-matched (PM) designs.¹⁰

Periimplant crevicular fluid (PICF), an osmotically mediated inflammatory exudate, originates from the periimplant gingival vessel plexus. The composition of PICF is similar to gingival crevicular fluid (GCF), consisting of cells, host-derived enzymes and their inhibitors, inflammatory mediators, host response modifiers, and tissue breakdown products. Changes in PICF flow rate and cytokine profiles may occur based on the health status of the periimplant mucosa. PICF analysis may help in detecting early metabolic and biomechanical lesions as well as in monitoring the osseointegration process.¹¹ Although PICF cytokine content has been studied in response to surgical trauma and in periimplantitis,^{12,13} there is no information on the PICF cytokine profile around PS implants. The purpose of this study was to investigate and compare soft tissue responses and PICF content between PS and PM implants during the early healing stage.

Materials and Methods

Study Population and Design

The study design was a nonrandomized, controlled, observational clinical trial. Patients seeking dental implant placement in 2 different quadrants were recruited from January to

December 2012 from the Graduate Periodontology Clinic at the Ohio State University. The inclusion criteria were (1) adult patients, aged 18–75 years; (2) non-smokers; (3) systemically and periodontally healthy. Exclusion criteria included (1) smokers; (2) immediate and/or one-stage implant placement; (3) untreated periodontal disease; (4) pregnant or lactating women; (5) history of bisphosphonate therapy (intravenous or oral for more than 3 years); (6) other systemic conditions or medications possibly affecting the surgical procedure and healing process. The study protocol was approved by the Institutional Review Board of The Ohio State University (protocol no. 2011H0355).

Implant Surgical Protocol

Each patient received 2 full Osseotite tapered Certain implants (either both 5.0 mm in diameter or one 5.0 mm and one 4.0 mm in diameter; BIOMET 3i, Palm Beach Gardens, FL). Both implants were placed at alveolar crest level and installed using a 2-staged (submerged) protocol, allowing 2 to 4 months of submerged healing time for osseointegration.

At second-stage surgery, mucoperiosteal flaps were elevated for both implants after an H-shaped incision to create 2 similar surgical sites. The healing abutments (Certain Bellatek Encode; BIOMET 3i) were inserted as follows: (1) if both implants were 5.0 mm in diameter, one was connected to a 4.1 mm diameter healing abutment (test group; PS) and the other to a 5.0 mm diameter healing abutment (control group; PM); the group selection was randomized by flipping a coin; (2) if 2 implants had different diameters (5.0 mm [PS] and 4.0 mm [PM]), both implants were connected to the same diameter healing abutments (4.1 mm). A standardized abutment height (4 mm) was used. The flap was repositioned with 4-0 silk using interrupted suturing technique. The implant uncovering surgery for both implants was completed at the same appointment and by the same surgeon (H.W.M.).

Clinical Measurements

At 1, 2, 4, and 6 weeks after the second-stage surgery, clinical periodontal parameters, including modified plaque index (mPI),¹⁴ modified sulcus bleeding index (mSBI),¹⁴ and probing depth (PD) were recorded on 6 sites per implant/abutment by a sole examiner (H.W.M.). PD was measured by the insertion of a calibrated plastic periodontal probe (Colorvue probe, UNC 12; Hu-Friedy, Chicago, IL) with a point diameter of 0.5 mm. The average of the 6 values was calculated to generate a single value per implant. The intraexaminer agreement was 0.78 (Cohen's kappa analysis).¹⁵

PICF Sampling

PICF samples were collected as described previously.¹⁶ In brief, implant sites were isolated with cotton rolls, gently air-dried, and visible supragingival plaque was removed. The PICF was collected from mesial and distal surfaces of each implant, at 1, 2, 4 and 6 weeks of healing, by the insertion of a sterile paper strip (PerioPaper; Proflow, Amityville, NY) into the periimplant sulcus until it encountered light resistance. The strip was then held in place for 30 seconds and transferred to a calibrated electronic volume quantification unit (Periotron 8000; Ora Flow, Plain View, NY) to determine the volume. The procedure was

repeated 5 minutes later with another paper strip at the same site. The 4 strips from each implant were pooled into an Eppendorf tube and stored at -20°C .

Multiplex Bead-Based Assays

The preparation of PICF elution was previously described.¹⁶ Multiplex bead-based assays were performed to study inflammatory mediators using a commercially available cytokine assay kit (Bio-Plex; Bio-Rad, Hercules, CA), allowing the determination of 20 cytokines: interleukin-1 receptor antagonist (IL-1ra), interleukin-4 (IL-4), IL-10, IL-12, IL-17, macrophage inflammatory protein-1 α (MIP-1 α), eotaxin, fibroblast growth factor (FGF), platelet derived growth factor (PDGF), RANTES (regulated on activation, normal T cell expressed and secreted), IL-1 β , IL-6, IL-8, MIP-1 β , tumor necrosis factor- α (TNF- α), vascular endothelial growth factor, interferon gamma-induced protein-10 (IP-10), interferon gamma, granulocyte colony-stimulating factor, and granulocyte/macrophage colony-stimulating factor.

Statistical Analysis

Computer software (SAS v. 9.2; SAS, Cary, NC and SPSS v. 20; IBM, Armonk, NY) was used to analyze clinical data and PICF cytokine expression. Between-group comparisons (PM vs PS) were analyzed at each time point, and within-group comparisons were examined between weeks 1 and 6. The analysis of PICF was completed for both concentration and total amount. A linear mixed-model regression analysis was used for repeated-measures fixed and random-effects within and between groups. Repeated-measures analysis of variance was used for within-group comparisons between weeks 1 and 6, and between-group comparisons (PM vs PS). Bonferroni correction was used to control the overall type I error at $\alpha = 0.05$. The results were considered statistically significant at a P -value < 0.05 .

Sample size of 16 per group was proposed to provide at least 95% power to detect the size of 1 SD change for each group at a significant level of 0.05 based on paired t tests. A total of 17 subjects were recruited, and 14 subjects were included in the analysis, which provided at least 93% power to detect such effect size.

Results

Study Population

A total of 17 patients fulfilled the inclusion criteria and were recruited. Fourteen patients (5 men and 9 women, aged 25–73 years; mean age: 58.7 years) completed the study protocol and provided complete sets of clinical recordings and PICF samples. Three subjects were excluded; 1 failed to comply with study protocol and 2 had early implant failure. Patient demographics and distribution of platform designs are presented in Table 1. For both PM and PS groups, 5 and 9 implants were localized in the maxilla and in the mandible, respectively. The PM group had 5, 8, and 1 implant(s) that replaced molars, premolars, and a canine, respectively; whereas the PS group had 12 and 2 implants that replaced molars and premolars, respectively. The implant diameter was 4 mm for most of the sites (10) in the PM group and was 5 mm for all implants in the PS group. Most of the implant lengths were

either 11.5 mm or 10 mm (12 sites in PM; 11 sites in PS). Only one patient received an 8 mm implant in both PM and PS groups.

Clinical Measurements and PICF Sampling

The soft tissue healing around PS and PM implants was followed through clinical parameters (mPI, mSBI, and PD), and PICF content during the first 6 weeks of healing after uncovering surgery and abutment installation (Figs. 1 and 2). A decrease in plaque accumulation throughout the study was noted in both PM and PS groups. The mPI for PS and PM at 1 week were 0.8 ± 0.2 and 0.6 ± 0.2 , respectively, and at 6 weeks, they were 0.4 ± 0.1 and 0.2 ± 0.1 , respectively. There was no significant difference between 1 and 6 weeks in either group ($P > 0.05$) (Fig. 2, A). Similarly, minimal gingival inflammation was noted throughout the study in both groups. The mSBI for PS and PM at 1 week were 0.2 ± 0.1 and 0.1 ± 0.1 , respectively; and at 6 weeks, they were 0.02 ± 0.02 and 0.1 ± 0.04 , respectively. There was no significant difference between 1 and 6 weeks in either group ($P > 0.05$) (Fig. 2, B). Differences between PM and PS at each time point were also not statistically significant ($P > 0.05$). A similar decrease pattern in both PM and PS groups was noted for PD (Fig. 2, C). In PM, the mean PD was 3.5 ± 0.4 mm at week 1 and 2.3 ± 0.1 mm at week 6, whereas in PS, the mean PD was 2.9 ± 0.2 mm at week 1 and 2.0 ± 0.1 mm at week 6. The differences in PD between week 1 and week 6 were statistically significant for both PM and PS groups ($P = 0.0005$ for both). In addition, the difference between PM and PS was statistically significant at week 1 only with PM group having deeper PD ($P = 0.03$).

PICF total volume collected in 30 seconds per strip is presented in Figure 2, D. As expected, PICF total volume in both PM and PS groups decreased from week 1 to 6. In PM, PICF total volume was 1.8 ± 0.25 μ L at week 1 and 1.4 ± 0.2 μ L at week 6, whereas in PS, PICF total volume was 2.0 ± 0.35 μ L at week 1 and 1.2 ± 0.24 μ L at week 6. This difference was statistically significant only for PS group ($P = 0.0005$). Between-group comparisons revealed no significant differences ($P > 0.05$), with almost overlapping values for PM and PS groups at each time point.

PICF Cytokine Content During Healing

Of the 20 cytokines tested, half were detected at very low levels with no differential expressions within and between groups (IL-1ra, IL-4, IL-10, IL-12, IL-17, MIP-1 α , eotaxin, FGF, PDGF, and RANTES; data not shown). The remaining 10 cytokines are reported in both concentration and total amount in Table 2. Reported statistical analysis is based on total amount; results for concentration were similar to results for total amount. IL-6 and MIP-1 β showed significant differences between weeks 1 and 6 in both PM and PS groups, whereas TNF- α was significantly different between weeks 1 and 6 only in PS. Moreover, significant differences between PM and PS groups was detected only for TNF- α ($P = 0.005$). For the remaining cytokines, the time- and group-dependent differences were negligible ($P > 0.05$).

The total IL-6 detected within PICF was drastically decreased from week 1 to 6 in both PM and PS groups (Fig. 3, A) (from 33 ± 7 pg to 0.4 ± 0.1 pg in PM and from 47 ± 15 pg to 1 ± 0.4 pg in PS; $P = 0.0005$ for both groups). There was no statistical difference between groups at any time point ($P > 0.05$).

A steady decrease in the level of MIP-1 β throughout the study was noted (Fig. 3, B). In the PM group, the total amount of MIP-1 β was 17 ± 3 pg at week 1 and 5 ± 1 pg at week 6 ($P = 0.03$). In the PS group, the MIP-1 β level was 21 ± 6 pg at week 1 and 6 ± 2 pg at week 6 ($P = 0.003$). There was no significant difference between groups at any time period ($P > 0.05$).

The TNF- α level of the PS group at week 1 was almost 3 times higher than that of the PM group (17 ± 7 pg vs 6 ± 1 pg, respectively; $P = 0.005$) (Fig. 3, C). A gradual decrease in PICF TNF- α during healing was noted for both groups, with no significant differences between groups at any time point after week 1 ($P > 0.05$). The decrease from week 1 to 6 observed in PS group was statistically significant (17 ± 7 pg to 4 ± 1 pg; $P = 0.001$), but not the one seen in PM group (6 ± 1 pg to 3 ± 1 pg; $P > 0.05$).

Discussion

Platform switching refers to the use of a smaller diameter abutment on a larger diameter implant body and has been shown to be associated with less crestal bone loss around the implant.¹⁷ However, the mechanism(s) responsible for the decreased crestal bone loss observed in PS implants has not been fully understood. The literature is lacking studies assessing the early healing events around PS implants. To the best of our knowledge, this is the first study exploring differential expression of various cytokines in PICF as a soft tissue response to PS versus PM implants during the early phases of healing.

Clinical parameters including mPI, mSBI, and PD were recorded at 1, 2, 4, and 6 weeks after implant uncovering surgery. There was a trend for deeper PD noted in the PM group, with a significant difference between PM and PS at week 1 ($P = 0.03$), but not at week 6, suggesting a transient change during healing. The initial shallower PD in the PS group may be a result of higher resistance to mechanical periimplant probing because of the inward shift of the implant-abutment junction and possible soft tissue folding around the abutment. In this study, the differences in PD between weeks 1 and 6 were statistically significant for both PS and PM groups ($P = 0.0005$). In week 6, the mean PD was 2.0 ± 0.1 mm in the PS group and 2.3 ± 0.1 mm in the PM group, similar to the PD in the control group reported by Lang et al.¹⁸ The mSBI was below 0.2 throughout the study in both groups, indicative of a very mild gingival inflammation. Although mPI and mSBI were stable, PICF total volume and proinflammatory cytokine levels suggested higher levels of inflammation at week 1 compared with week 6. This was expected as the post-wounding inflammation should decrease with time. This is in agreement with previous findings that PICF volume and cytokine levels were high at week 1 after implant placement and significantly decreased thereafter.^{16,19}

The purpose of this study was to investigate whether platform switching would differentially affect soft tissue responses of periimplant tissues after second-phase uncovering surgery. The results show that although soft tissue manipulation through surgical procedures induces a significant inflammatory response, platform switching by itself does not differentially affect this response. It has been documented that the magnitude of cytokine elevation may be associated with the extent of tissue trauma and severity of tissue injury.²⁰ In this study, the effects of surgical trauma on healing response were limited by creating similar wound sizes

at each quadrant in the same surgical setting by the same clinician. Regardless of the amount of keratinized gingiva, an “H-shaped” incision was made with minimal periosteal flap elevation to expose the implant. The study began at the implant uncovering surgery, with an observation time up to 6 weeks postoperatively. Previous studies have shown that major changes in clinical parameters and local cytokine levels during early wound healing occur in the first 3 weeks of healing after implant placement,¹⁶ and periimplant soft tissue clinical maturity can be established as early as 4 weeks.²¹

The analysis of PICF content in this study was completed for both concentration and total amount, but data were reported based on the total amount because the results between the two analyses were similar. Concerns have been raised about the manner to interpret data that report the levels of crevicular fluid. It has been shown that the total amount (or activity), not the concentration, of the mediator in the crevicular fluid sample can be reported when timed samples are collected.²² The total amount is a reproducible way to examine the GCF level and has been the preferred method to analyze the content of GCF. Unlike serum samples, where the sample is a small part of the total fluid volume, GCF samples often collect the entire volume of fluid at the sample site.²³ In addition, the strip must remain in the sulcus long enough to obtain an adequate volume of fluid. Previous studies have developed an approach to GCF sampling that standardizes the time of collection and reports the data as the total amount in the timed sample.²⁴

Among the 10 cytokines that were analyzed, only IL-6, MIP-1 β , and TNF- α showed significant differences. IL-6 is an important cytokine involved in the regulation of host response to tissue injury and infection.^{25–29} MIP-1 β , also known as CC-chemokine ligand 4 (CCL4), is a CC-chemokine with specificity for CCR5 receptors.³⁰ It is produced by macrophages after they are stimulated with bacterial endotoxins,³¹ and is a chemoattractant for natural killer cells, monocytes, and other immune cells.³² TNF- α is a cytokine produced mainly by macrophages.³³ It has been implicated in the periodontal disease process because of its ability to stimulate bone resorption and other catabolic processes.³⁴ This study reports a significant decrease in the TNF- α level between weeks 1 and 6 in PS ($P=0.001$), but not in PM. In addition, TNF- α was the only cytokine that showed a significant difference between PM and PS groups in this study ($P=0.005$). According to Petkovic et al.,³⁵ a positive correlation was noted between TNF- α levels and the extent of periimplant inflammation. The TNF- α level of the PS group at week 1 was almost 3 times higher than that of the PM group, indicating a higher inflammatory response in the PS group during early wound healing. The possible exposure of the soft tissues to a portion of the seating platform (minimally rough surface) in the PS group may contribute to higher levels of initial inflammatory response. This speculation is supported by the previous finding that a roughened coronal surface may cause activation of inflammatory cells.^{36,37} However, this explanation for the higher TNF- α levels in the PS group remains to be proven. It is worth noting that some anti-inflammatory mediators, such as IP-10, showed a statistically nonsignificant increase in total amount, concomitant with the observed decrease in potent proinflammatory cytokines (Table 2).

Two-stage implant placement protocol was implemented in this study. Our results have demonstrated that there are strong similarities in soft tissue response between one-¹⁶ and 2-

stage protocols in regard to total amount of PICF produced and cytokine expression pattern. In our study, not only were the total amount of PICF and cytokine levels of IL-6 and MIP-1 β not significantly different to those found in one-stage protocols but also their productions were high at week 1 after surgery before decreasing significantly during early soft tissue healing. These observations indicate that periimplant soft tissue responses were not significantly different between one- and 2-stage implant placements. However, this study is designed to detect large effect size (1 SD difference) between PM and PS implants; further studies with larger sample sizes may find significant differences for a smaller effect size. Also, because each patient received both PM and PS implants in this study, the difference between PM and PS may be confounded with the individual response, and a different study design to compare the patients with PM or PS alone may also yield different results.

Conclusion

To our knowledge, this is the first study reporting the proinflammatory cytokine expression in the PICF of PS implants during early soft tissue healing after abutment installation and comparing against PM implants. Within the limits of this study, it seems that periimplant soft tissue response around PM and PS implants is mostly similar with time- and mediator-specific differences during the early healing period.

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Fig. 1. Clinical images of a case during a 6-week healing period. (A) PS site and (B) PM site. 1, 2, 4, and 6 weeks indicates 1, 2, 4, and 6 weeks after implant uncovering surgery; Baseline; at the end of implant uncovering surgery; F, facial view; O, occlusal view.

Fig. 2. Clinical measurements at 1, 2, 4, and 6 weeks after implant uncovering surgery. **(A)** mPI, **(B)** mSBI, **(C)** PD, and **(D)** PICF total volume. *Statistically significant differences between week 1 and week 6 in PS ($P = 0.0005$); **Statistically significant differences between week 1 and week 6 in PM ($P = 0.0005$); ***Statistically significant differences between PS and PM at week 1 ($P = 0.03$).

Fig. 3.

Expression of cytokines IL-6, MIP-1 β , and TNF- α in PM or PS groups. (A) IL-6, (B) MIP-1 β , and (C) TNF- α . *Statistically significant differences between week 1 and week 6 in PS ($P=0.0005$). **Statistically significant differences between week 1 and week 6 in PM ($P=0.0005$); #Statistically significant differences between week 1 and week 6 in PS ($P=0.003$); ##Statistically significant differences between week 1 and week 6 in PM ($P=0.03$); @Statistically significant differences between week 1 and week 6 in PS ($P=0.001$); @@Statistically significant differences between PS and PM at week 1 ($P=0.005$).

Table 1

Demographics and Platform Design of Study Population

Demographic Characteristics		
Patients (n)	14	
Sex (males/females)	5/9	
Age (y)		
Range	25–73	
Mean $\pm$ SE	58.7 $\pm$ 13.8	
Platform Design	PM	PS
Jaw location (maxilla/mandible)	5/9	5/9
Tooth type (molar/premolar/canine)	5/8/1	12/2/0
Implant diameter (4 mm/5 mm)	10/4	0/14
Implant length (8 mm/10 mm/11.5 mm/13 mm)	1/4/8/1	1/6/5/2

Table 2

Cytokine Levels in the PICF of PM or PS Implants

Cytokines	Week 1		Week 2		Week 4		Week 6	
	PS	PM	PS	PM	PS	PM	PS	PM
IL-1 β (pg) *								
Mean $\pm$ SE	25 $\pm$ 6	23 $\pm$ 3.4	11 $\pm$ 3	13.4 $\pm$ 5	8.3 $\pm$ 1.6	8.2 $\pm$ 3.2	10 $\pm$ 2	5 $\pm$ 1
Median (range)	15 (2–69)	20 (6–52)	7 (1–38)	8 (1.3–64)	8 (1–20)	4 (1–43)	11 (1–20)	4 (1–14)
IL-1 β (ng/mL) †								
Mean $\pm$ SE	12 $\pm$ 2.4	13 $\pm$ 1.3	8 $\pm$ 1.8	9 $\pm$ 3	7 $\pm$ 1.2	9.1 $\pm$ 3.2	7.9 $\pm$ 1.3	9.6 $\pm$ 6.2
Median (range)	10 (2–31)	14 (5.4–19)	8 (1–26)	6 (1.4–37)	5.3 (1–15)	4.3 (1–44)	8.6 (1–14)	3 (2–90)
IL-8 (pg) *								
Mean $\pm$ SE	157 $\pm$ 40	192 $\pm$ 32	61 $\pm$ 17	46 $\pm$ 8	43 $\pm$ 14	38 $\pm$ 9	51 $\pm$ 11	48 $\pm$ 7
Median (range)	124 (40–494)	193 (44–457)	32 (4–193)	41 (9–103)	32 (6–212)	37 (5–119)	41 (15–128)	31 (4–253)
IL-8 (ng/mL) †								
Mean $\pm$ SE	223 $\pm$ 117	133 $\pm$ 16	50 $\pm$ 13	35 $\pm$ 5	37 $\pm$ 11	33 $\pm$ 7	43 $\pm$ 9	40 $\pm$ 17
Median (range)	54 (35–1684)	130 (44–269)	26 (2–141)	35 (9–75)	28 (6–167)	23 (5–93)	29 (15–98)	25 (5–253)
IL-6 (pg) *								
Mean $\pm$ SE	47 $\pm$ 15	33 $\pm$ 7	7 $\pm$ 3	4 $\pm$ 2	1 $\pm$ 0.3	2 $\pm$ 1	1 $\pm$ 0.4	0.4 $\pm$ 0.1
Median (range)	31 (0.2–172)	31 (0.3–75)	1 (0–39)	0.7 (0–21)	0.3 (0.2–4)	0.3 (0.1–13)	0.4 (0–5.4)	0.3 (0–1.5)
IL-6 (ng/mL) †								
Mean $\pm$ SE	19 $\pm$ 6	18 $\pm$ 3.5	5 $\pm$ 2	3 $\pm$ 1	1 $\pm$ 0.2	1 $\pm$ 0.7	1 $\pm$ 0.4	0.4 $\pm$ 0.1
Median (range)	12 (0.3–77)	19 (0.3–46)	1.3 (0–21)	0.5 (0.1–3)	0.3 (0.1–10)	0.3 (0–10)	0.5 (0.1–5)	0.3 (0–1.8)
MIP-1 β (pg) *								
Mean $\pm$ SE	21 $\pm$ 6	17 $\pm$ 3	11 $\pm$ 6	7 $\pm$ 2	7 $\pm$ 4	5 $\pm$ 1	6 $\pm$ 2	5 $\pm$ 1
Median (range)	7 (1.4–74)	16 (3–39)	3 (0–91)	4 (1–25)	3 (1–59)	5 (1–13)	3 (1–24)	3 (1–14)
MIP-1 β (ng/mL) †								
Mean $\pm$ SE	9 $\pm$ 3	10 $\pm$ 1.3	9 $\pm$ 5	5 $\pm$ 1.4	6 $\pm$ 3	4 $\pm$ 1	5 $\pm$ 2	3 $\pm$ 1
Median (range)	4 (2–33)	9 (3–20)	3 (1–61)	4 (1–21)	3 (0.4–46)	3 (0.4–13)	4 (1.2–21)	2.4 (1–10)
TNF- α (pg) *								

Cytokines	Week 1		Week 2		Week 4		Week 6	
	PS	PM	PS	PM	PS	PM	PS	PM
Mean $\pm$ SE	17 $\pm$ 7	6 $\pm$ 1	5 $\pm$ 1	3.4 $\pm$ 0.5	3 $\pm$ 1	3 $\pm$ 0.4	4 $\pm$ 1	3 $\pm$ 1
Median (range)	6 (1.4–76)	5 (3–14)	3 (1–19)	3 (1.5–8)	2 (1.5–13)	3 (1–7)	2.4 (1.3–13)	2 (1–15)
TNF- α (ng/mL) [†]								
Mean $\pm$ SE	21 $\pm$ 4	24 $\pm$ 3	23 $\pm$ 4	22 $\pm$ 3	28 $\pm$ 4	32 $\pm$ 6	25 $\pm$ 5	25 $\pm$ 6
Median (range)	19 (7–62)	23 (7–44)	23 (0.4–50)	18 (8–45)	29 (10–58)	25 (6–84)	20 (12–78)	16 (9–95)
VEGF (pg) [*]								
Mean $\pm$ SE	38 $\pm$ 6	39 $\pm$ 4	30 $\pm$ 5	31 $\pm$ 3	31 $\pm$ 3	33 $\pm$ 4	27 $\pm$ 3	30 $\pm$ 6
Median (range)	30 (10–78)	37 (22–71)	26 (1–62)	30 (16–46)	31 (10–54)	36 (10–57)	27 (15–43)	27 (15–43)
VEGF (ng/mL) [†]								
Mean $\pm$ SE	21 $\pm$ 4	24 $\pm$ 3	23 $\pm$ 4	22 $\pm$ 4	28 $\pm$ 4	32 $\pm$ 6	25 $\pm$ 5	25 $\pm$ 6
Median (range)	19 (7–62)	23 (7–44)	23 (0.4–50)	18 (8–45)	29 (10–58)	25 (6–84)	20 (12–78)	16 (9–95)
IP-10 (pg) [*]								
Mean $\pm$ SE	9 $\pm$ 2	8 $\pm$ 1	8 $\pm$ 2	7 $\pm$ 1	12 $\pm$ 3	13 $\pm$ 4	16 $\pm$ 5	13 $\pm$ 3
Median (range)	6 (3–17)	6 (4–15)	7 (1–21)	8 (2–13)	9 (2–32)	8 (3–58)	8 (3–73)	12 (2–38)
IP-10 (ng/mL) [†]								
Mean $\pm$ SE	5 $\pm$ 1	4 $\pm$ 0.4	6 $\pm$ 1.5	11 $\pm$ 7	17 $\pm$ 5	11 $\pm$ 4	14 $\pm$ 4	11 $\pm$ 2
Median (range)	4.5 (2–9)	4 (2–7)	5 (1–20)	4 (2–90)	9 (2–74)	7 (2–61)	8 (3–60)	9 (2–29)
G-CSF (pg) [*]								
Mean $\pm$ SE	24 $\pm$ 5	21 $\pm$ 2	12 $\pm$ 3	14 $\pm$ 3	13 $\pm$ 2	12 $\pm$ 2	18 $\pm$ 3	12 $\pm$ 2
Median (range)	18 (4–74)	21 (5–32)	9 (2–31)	13 (2–36)	10 (5–29)	11 (1–34)	15 (4–44)	12 (3–24)
G-CSF (ng/mL) [†]								
Mean $\pm$ SE	11 $\pm$ 2	13 $\pm$ 2	10 $\pm$ 2	10 $\pm$ 2	12 $\pm$ 2	11 $\pm$ 2	15 $\pm$ 3	9 $\pm$ 1
Median (range)	8 (3–33)	11 (6–23)	7 (1–36)	7 (2–36)	11 (2–23)	10 (1–29)	11 (3–38)	9 (2–17)
GM-CSF (pg) [*]								
Mean $\pm$ SE	8 $\pm$ 2	10 $\pm$ 2	12 $\pm$ 2	13 $\pm$ 2	13 $\pm$ 2	14 $\pm$ 2	11 $\pm$ 2	13 $\pm$ 2
Median (range)	6 (3–23)	8 (4–24)	11 (3–26)	11 (3–27)	10 (7–25)	10 (7–26)	10 (7–24)	10 (6–25)
GM-CSF (ng/mL) [†]								
Mean $\pm$ SE	6 $\pm$ 2	7 $\pm$ 2	11 $\pm$ 2	12 $\pm$ 2	13 $\pm$ 3	16 $\pm$ 4	13 $\pm$ 4	13 $\pm$ 3

Cytokines	Week 1			Week 2			Week 4			Week 6		
	PS	PM		PS	PM		PS	PM		PS	PM	
Median (range)	3 (2–24)	7 (2–17)		11 (1–19)	13 (1–26)		11 (4–32)	10 (4–45)		8 (6–49)	10 (5–35)	
INF- γ (pg) [*]												
Mean $\pm$ SE	9 $\pm$ 2	10 $\pm$ 2		8 $\pm$ 3	10 $\pm$ 3		6 $\pm$ 1	7 $\pm$ 1		8 $\pm$ 2	6 $\pm$ 1	
Median (range)	7 (2–33)	7 (3–27)		6 (0–43)	8 (3–41)		7 (2–13)	7 (0–18)		6 (0–27)	5 (0–16)	
INF- γ (ng/mL) [†]												
Mean $\pm$ SE	6 $\pm$ 1	6 $\pm$ 1		6 $\pm$ 1	7 $\pm$ 1		6 $\pm$ 1	6 $\pm$ 1		7 $\pm$ 2	5 $\pm$ 1	
Median (range)	5 (2–17)	6 (1–13)		5 (0–19)	5 (1–22)		5 (1–11)	6 (0–13)		5 (0–27)	5 (0–14)	

^{*} PICF content was reported in total amount.
[†] PICF content was reported in concentration.

G-CSF indicates granulocyte colony–stimulating factor; GM-CSF, granulocyte/macrophage colony–stimulating factor; IFN- γ , interferon gamma; VEGF, vascular endothelial growth factor.