Original Article

Clinical and Biochemical Effects of Erbium, Chromium: Yttrium, Scandium, Gallium, Garnet Laser Treatment as a Complement to Periodontal Treatment

K Üstün, M Hatipoğlu, Ö Daltaban, R Felek[1], MZ Firat[2]

Departments of Periodontology and [1]Basic Science, Faculty of Dentistry, Akdeniz University, [2]Department of Genetics and Biometrics, Faculty of Agriculture, Akdeniz University, Antalya, Turkey

Abstract

Objective: The purpose of this study was to investigate the clinical effects of erbium, chromium: yttrium, scandium, gallium, garnet (Er, Cr: YSGG) laser treatment as a complementary to scaling and root planning (SRP) during the treatment of chronic periodontitis and gingival crevicular fluid (GCF) interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and interleukin-35 (IL-35) levels. **Materials and Methods:** Forty patients with chronic periodontitis were divided into two equal groups at random to receive SRP alone and SRP followed by Er, Cr: YSGG laser treatment, which are control and test groups, respectively. Clinical attachment level (CAL), probing depth (PD), bleeding on probing (BOP), gingival index (GI), and plaque index (PI) were measured for all patients in both groups at baseline and again at the end of the 1st, 3rd, and 6th months following the treatment. Levels of GCF IL-1β, IL-6, and IL-35 were analyzed by enzyme-linked immunosorbent assay. **Results:** After periodontal treatment, CAL, PD, BOP, GI, and PI, which are clinical parameters analyzed, decreased significantly ($P < 0.05$) in both test and control groups. GCF volume, IL-1 β, IL-6, and IL-35, levels in both groups proved statistically significant reductions compared to the baseline ($P < 0.05$), but no substantial variations were detected among both groups. **Conclusion:** According to these results, we can suggest that IL-35 may be related to the pathogenesis of periodontitis and that Er, Cr: YSGG laser can be used as an adjunct to SRP in periodontal treatment.

Keywords: *Erbium, chromium: yttrium, scandium, gallium, garnet laser, interleukin-35, periodontitis*

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Introduction

Periodontal disease is characterized by chronic inflammation of the supporting periodontal tissues, which is mediated by the host immune and inflammatory response to the microbial dental plaqueflora.[1] Elimination of supra- and subgingival bacterial deposits is the basic and long-term aspect of periodontal treatment for preventing the progression of disease and maintaining the periodontal health.[2] Scaling and root planning (SRP) is commonly used as a nonsurgical periodontal treatment method and its clinical efficacy has been demonstrated in several clinical studies.[3,4] Mechanical periodontal treatment alone, on the other hand, is not all the time prognosticated and has some limitations for completely eradicating pathogenic bacteria and toxins within deep periodontal pockets and in complex root morphologies that are inaccessible by periodontal instruments.[5,6] Furthermore, mechanical instrumentations have been shown to produce a smear layer that contains microbiota and its products that may affect the periodontal healing and can lead to residual periodontal pocketing and bacterial recolonization.[6,7]

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Address for correspondence: Prof. M Hatipoğlu, Department of Periodontology, Akdeniz University, Faculty of Dentistry, 07058 Antalya, Turkey.
E-mail: mukerremhatipoglu@hotmail.com

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To overcome these limitations and improve the effectiveness of the treatment, new technical modalities, such as laser systems, have also been used as a complementary or alternative therapy to mechanical periodontal treatment due to several advantages.[8-10] The erbium, chromium: yttrium, scandium, gallium, garnet (Er, Cr: YSGG) laser (2.78 mm), which has an active medium of YSGG doped with chromium and erbium and emits free-running pulsed laser energy at 2780 nm, has been successfully used in periodontal treatment.[11,12] Several studies have shown that this laser, in a suitable wavelength, promotes calculus removal without thermal damages and may effectively remove smear layer and have strong bactericidal effects to reduce the amount of the bacterial population in the periodontal pocket.[11-13]

However, the anti-inflammatory and antimicrobial effects of laser treatment on the periodontal tissue are still not completely understood. Microbial agents that host immune responses and environmental factors collectively provoke host responses and result in releasing biologic mediators such as cytokines.[14] Increase in cytokine production results in periodontal tissue damage, and various cytokines have been detected in gingival crevicular fluid (GCF).[15]

IL-6, which is generated by host cells, is a valuable cytokine in the regulation of host response and it has a key function in B-cell differentiation, T-cell proliferation and also IL-6 is synergistic with interleukin-1 beta (IL-1 β) that induces bone resorption.[16,17] The proinflammatory cytokine IL-1 β also adjusts prostaglandins production, as well as encouraging the formation of osteoclasts and bone resorption.[18] IL-1 β has been demonstrated to be considerably reproduced in the periodontal tissues and also gingival fluid from diseased areas considering the healthy areas. Monitoring IL-1 β levels was suggested in order to compare treatment outcomes by many authors.[14,15,19]

IL-35, the newest member of IL-12 cytokine family, is a potent inhibitory cytokine produced by natural, thymus-derived regulatory T-cell (nTreg) populations.[20] It has been reported that IL-35 inhibits T-cell proliferation, induces the development of an induced regulatory T-cell (iTreg) population, and also suppresses T-cell proliferation by inducing cell cycle arrest in G_1 without inducing apoptosis.[20-22] More recently, it has been shown that IL-35 appears to take part like an immunomodulatory agent in many disease cases.[23,24] The expression of IL-35 mRNA in gingival tissues and GCF levels in chronic periodontitis versus healthy has been demonstrated and it has been suggested that IL-35 is associated with the pathogenesis of periodontitis.[25,26] In our literature review, however, there was no study comparing the effects of periodontal treatment on GCF IL-35 levels. Being able to potentially influence the advancement of periodontal disease, proinflammatory cytokines can also determine clinical treatment's effectiveness. The aim of this study was to investigate the effects of laser treatment (Er,Cr:YSGG) in chronic periodontitis patients using clinical parameters and GCF IL-1β, IL-6, and IL-35 levels.

Materials and Methods

The study carried out was a controlled and randomized clinical trial using a parallel design. Forty patients, who have chronic periodontitis and were referred to the Department of Periodontology, Faculty of Dentistry, Akdeniz University, for periodontal treatment, were appointed in two groups of equal number by a random selection to get SRP and laser (test group) or SRP alone (control group). Coin toss method was used for randomization. Table 1 represents the demographic characteristics of the study groups.

While written consent of all individuals was taken before the study, the protocol submitted to Akdeniz University Ethics Committee (2014-180) for the participation of human subjects has been accepted.

Patients having at least 2 teeth with ≥5 mm probing pocket depth (PPD) were included in every quadrant provided that they had at least 14 teeth in their mouths. The exclusion criterion was a history of any systemic diseases that may influence the periodontal therapy outcome, for example, diabetes mellitus, cancer, metabolic or endocrine diseases, smoking, dental treatment in the past 6 months, antibiotic medication during the 6 months preceding the study, and related teeth with restoration.

Treatment protocols and laser parameters

All patients received periodontal therapy at first which consisted of comprehensive instructions on oral hygiene and supragingival scaling for the whole mouth with the combined use of hand (Hu-Friedy, Chicago, IL, USA) and ultrasonic instruments (EMS, Nyon, Switzerland). Each treatment was carried out 1 week apart. SRP was performed in a single appointment under local anesthesia. For laser groups, laser was applied in the same appointment. Er, Cr: YSGG laser (Waterlase® iplus, Biolase, Irvine CA, USA) treatment was performed with a RFPT 5–14 tip at 1.5 W 30 Hz, 15% Air, 15% H_2O H mode (pulse duration 140 ms). During the application of laser treatment, protective goggles were used both by the patient and by the operator.

Periodontal examination

Clinical periodontal parameters were evaluated at the baseline and after 1, 3, and 6 months following the treatment. The patients' periodontal statuses were assessed using thorough standard periodontal parameters. The assessed parameters were clinical attachment level (CAL), probing depth (PD), plaque index (PI),[10] and gingival index (GI).[11] While PD is specified as the measurement between the bottom of the periodontal pocket and the free gingival margin, CAL is defined as the measurement from bottom of the periodontal pocket to cementoenamel junction. These distance measurements of PD and CAL were recorded by a manual periodontal probe at six points (mesiobuccal, midbuccal, distobuccal, mesiolingual, midlingual, and distolingual) around each tooth (PWD, Hu-Friedy, Chicago, IL, USA).

Gingival crevicular fluid sampling

At the baseline and after 1, 3, and 6 months, GCF samples were compiled from the same tooth of every quadrant. The collections were performed as previously described by Köseoğlu *et al*., and as soon as the samples were collected, they were immediately stored at −20°C before analysis.[26]

During the analysis of GCF samples for IL-1 β (Invitrogen™ Corporation 542 Flynn Road, Camarillo, CA, USA), IL-35 (Uscn Life Science Inc., Wuhan, China), and IL-6 (DIAsource ImmunoAssays S. A.-Rue de l'Industrie, 8-B-1400, Nivelles, Belgium), a commercial kit was used in line with the instructions of the manufacturer. The plate was analyzed at a wavelength of 450 nm using an enzyme-linked immunosorbent assay reader (SEAC RADIM Company, Sirios model EAC, via di Prato, 72–74, Firenze, Italy).

Statistical analysis

SAS version 9.3 (SAS Institute, Cary, NC, USA), which is a commercially available software, was used for the statistical analysis. Descriptive statistics, such as the average and standard deviation (SD), were used to describe the main variables. The Shapiro–Wilks normality test was conducted to assess the variables' normality to use a parametric or nonparametric test. Parametric tests had been used within the groups (repeated measures analysis of variance/Tukey's test) and between the groups (two-tailed paired Student's *t*-test) during testing (whole-mouth clinical variables/site-specific clinical variables and all biochemical variables) since all variables were normally distributed. Associations between the whole-mouth clinical variables/site-specific clinical variables and all biochemical variables were investigated using Pearson's correlation test. A two-sided $P < 0.05$ was considered statistically significant for all analysis.

Results

All the data were entered, checked for missing values, and analyzed using the statistical methods described in the previous section. Table 1 illustrates the baseline demographic data of 40 patients participated in the study, where 19 patients were female and 21 patients were male. Average ages of patients in control and test groups were 44.05 and 45.80, respectively.

The statistical results of the clinical measurements, such as probing depth (PD), CAL, PI, GI, and bleeding on probing (BOP) as average ± SD, in test and control groups between baseline and 1st, 3rd, and 6th months are both presented in Table 2 and Figure 1, respectively. As shown in Table 1, all whole-mouth clinical variables represented statistically significant reductions at all given times compared to baseline in both test group and control group ($P < 0.05$). Comparing the average values at the 1st month, significant reductions were observed in the average values of GI and BOP at the 6th month for both groups. The changes in BOP after the 1st and 3rd months were also substantially higher for both groups ($P < 0.05$). On the other hand, the change in GI after the 1st and 3rd months was only significantly higher for the control groups ($P < 0.05$). At the 3rd month, the average values of BOP were also substantially higher than the average values recorded at the 6th month for both groups.

In a comparison between control and test groups, only PD decreased for the test group ($P < 0.05$). In test group, the decrease of PD at the 1st month was statistically substantial compared to the control group.

The results of the biochemical and sampled-site clinical measurements (IL-1 β, IL-6, IL-35, GCF volume [GCFvol], PD, CAL, PI, and GI as average ± SD) are illustrated for the test and control groups in Table 3. Average values of IL-1 β, IL-6, GCFvol, PD, CAL, PI, and GI at baseline were substantially lower for both groups than the average values at the 1st, 3rd, and

Table 1: Baseline demographic data

	Control group	Test group
Number of cases (*n*)	20	20
Gender		
Male	12	9
Female	8	11
Age (years)		
Mean±SD	45.80±6.53	44.05±6.16
Minimum	35	36
Maximum	58	59

SD=Standard deviation

Table 2: Full-mouth clinical variables of study group

Time	Group	PD	CAL	PI	GI	BOP
Baseline	Test	3.880±0.496	2.690±0.467	1.715±0.323	1.820±0.361	74.750±7.587
	Control	3.970±0.722	2.875±0.576	1.775±0.348	1.890±0.273	77.300±7.644
1 month	Test	2.180±0.897[a]	1.815±0.347	1.295±0.307	1.285±0.203	48.950±9.023
	Control	2.875±0.563	2.170±0.586	1.355±0.291	1.305±0.132	50.100±8.807
3 month	Test	2.065±0.768	1.705±0.496	1.170±0.159	1.200±0.141	40.950±10.694
	Control	2.210±0.533	1.990±0.757	1.250±0.150	1.155±0.132	41.050±9.709
6 month	Test	1.825±0.797	1.760±0.558	1.320±0.158	1.120±0.115	26.850±7.386
	Control	2.025±0.729	1.755±0.574	1.206±0.154	1.125±0.121	32.700±7.554

[a]Significant difference compared to test group $P<0.05$, Values are given as mean±SD; comparisons by means of paired *t*-test. PD=Probing depth; CAL=Clinical attachment level; PI=Plaque index; GI=Gingival index; BOP=Bleeding on probing; SD=Standard deviation

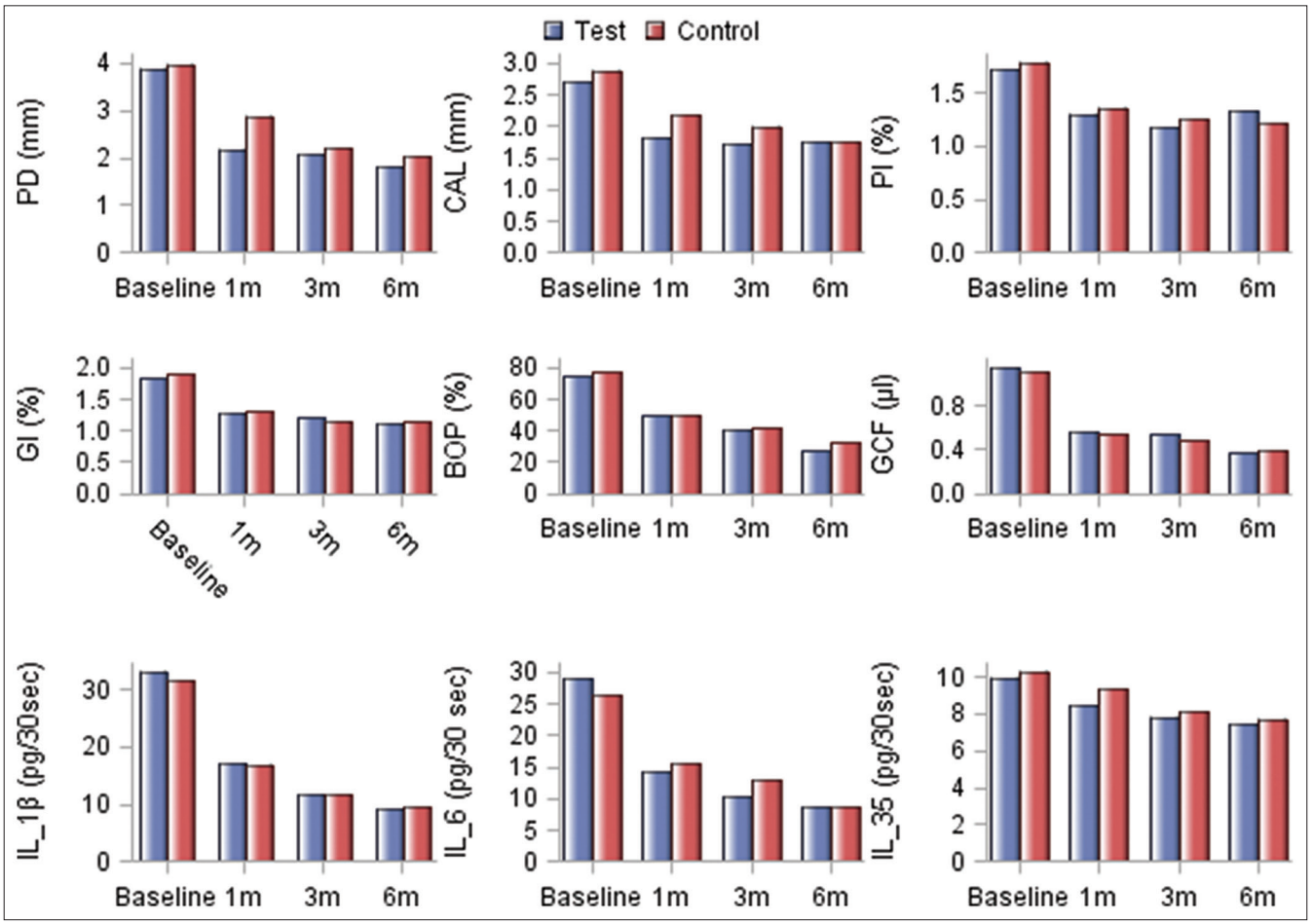

Figure 1: Whole-mouth probing depth, clinical attachment level, plaque index, gingival index, bleeding on probing (percent) values and gingival crevicular fluid volume and interleukin-1 beta, interleukin-6, and interleukin-35 values

6th months. No statistically significant differences were observed in IL-35 values between the time points in both groups. The change in IL-1 β, IL-6, GCFvol, PDs, and CALs after the 1st and 6th months and change in CALs at the same time points were considerably higher in test and control groups ($P < 0.05$). Furthermore, the change in PDs for the test group and change in GIs for the control group at months 1 and 3 were statistically substantial ($P < 0.05$). In a comparison between the 1st and 6th months, considerable differences were detected in GCFvol, CALs, and GIs values for the test group and also the average values of PDs and GIs after 3rd and 6th months were considerably lower in the control group.

Considering IL-1 β, IL-6, IL-35, GCFvol, PD, CAL, and PI parameters, there were no significant differences between test and control groups at any given time during the study [Table 3]. However, the decrease in GI was dramatically superior at the test group ($P < 0.05$). Substantial differences were observed between both groups at the 1st and 3rd months.

Table 3: Biochemical variables of study group

Time	Group	IL-1β	IL-6	IL-35	GCFvol	PDs	CALs	PIs	GIs
Baseline	Test	32.910±14.044	28.955±10.314	9.940±6.451	1.140±0.237	5.945±0.946	4.735±0.396	2.165±0.499	2.120±0.322
	Control	31.340±8.184	26.375±13.397	10.230±7.734	1.110±0.229	5.895±1.058	4.795±0.589	2.220±0.461	2.295±0.239
1 month	Test	17.085±7.360	14.140±9.017	8.450±4.894	0.565±0.213	4.005±0.909	2.755±0.730	1.415±0.434	1.335±0.146[a]
	Control	16.855±8.857	15.620±9.790	9.305±4.698	0.535±0.195	3.685±0.657	3.005±0.523	1.340±0.226	1.675±0.263
3 month	Test	11.620±7.553	10.420±7.930	7.805±2.774	0.540±0.233	3.160±0.529	2.395±0.522	1.400±0.189	1.285±0.118[a]
	Control	11.665±8.995	12.830±9.490	8.085±3.341	0.480±0.154	3.220±0.732	2.205±0.664	1.205±0.105	1.205±0.089
6 month	Test	8.975±6.648	8.655±6.760	7.380±3.228	0.370±0.163	2.695±0.555	2.015±0.497	1.460±0.173	1.440±0.135
	Control	9.420±8.634	8.715±4.659	7.700±3.099	0.395±0.132	2.700±0.725	2.145±0.579	1.370±0.203	1.400±0.162

[a]Significant difference compared to test group ($P<0.05$). Values are given as mean±SD; comparisons by means of paired *t*-test. IL=Interleukin; GCFvol=Gingival crevicular fluid; PDs=Probing depth; CALs=Clinical attachment level; PIs=Plaque index; GIs=Gingival index; SD=Standard deviation

Discussion

Clinically, SRP with hand instruments have been proven as an effective treatment method for periodontal disease.[3,4] The results of the study performed illustrated that periodontal treatment with either SRP alone or SRP followed by Er, Cr: YSGG laser treatment leads to both statistically and clinically important advancements in all analyzed clinical parameters (PI, GI, PD, BOP, and CAL) at the 1st, 3rd, and 6th months following treatment compared to baseline. Postoperative recovery was event free in all of the cases, which shows that nonsurgical periodontal treatment with SRP alone or in combination with Er, Cr: YSGG laser is well tolerated.

However, recent studies have demonstrated that complete removal of calculus and elimination of the microorganisms in the soft tissue wall of the pocket by manual instruments was often incomplete, and such treatment generally resulted in a smear layer, which holds bacteria and their products that may stimulate the process of periodontal tissue healing, on the surfaces of the root.[5-7]

To overcome these disadvantages, laser system gains popularity in general dental practice and is suggested as a complementary or alternative method for periodontal treatment.[8-10] Erbium family of lasers have been reported to be the most promising lasers for nonsurgical periodontal treatment.[9-11] The effects of different power outputs of Er, Cr: YSGG laser on the root surfaces and the efficiency of calculus removal were examined by Ting *et al*.,[13] and the authors reported that a 1 W power output setting is suitable for root scaling and removing calculus without making any morphologic alterations on the root surface. Hakki *et al*.[27] compared the mechanical treatment to Er, Cr: YSGG laser treatment for removing calculus and reported that laser therapy was effective on root surface ablation and could be practiced to achieve SRP during the course of periodontal disease treatment.

Practicing the Er, Cr: YSGG laser with root planning and scaling brought on statistically dramatic reductions of the full-mouth and site-specific probing depths (PD, PDs) compared to the outcomes achieved in SRP alone in 6 months after the treatment in the study performed. Furthermore, the site-specific CAL (CALs) improvement in the laser-treated group was statistically significant at 6 months after the treatment. This finding is in consistence with the results obtained from the previous studies.[28-30] In a 2-year follow-up study, Crespi *et al*.[28] found significant difference in the PD to favor Er: YAG treatment over conventional treatment with ultrasonic devices. Dyer and Sung[29] demonstrated that Er, Cr: YSGG surgical laser treatment along with a standard conventional treatment in every 3 months in moderate-to-advanced periodontal disease brought on a serious reduction in pocket depths and also improved levels of clinical attachment 2 years posttreatment. In a 1-year clinical study, Kelbauskiene *et al*.[30] compared SRP with Er, Cr: YSGG laser treatment in adjunct to SRP in patients with early-to-moderate periodontitis and showed that the average PD decrease and CAL increase were dramatically higher in SRP + laser-treated sites than in only SRP-treated sites and the most significant alterations of the PD were achieved in 6 months after the therapy.

In an *in vitro* study, Hakki *et al*.[12] concluded that the micromorphology of the root surfaces prepared by laser may be more satisfactory for the repair of the periodontal attachment by showing that the surfaces prepared by laser were more biocompatible for periodontal fibroblast attachment compared to curette-treated root surfaces. Our results are in agreement with this notion and may suggest that since several studies demonstrated that Er, Cr: YSGG laser has bactericidal effects and can effectively remove calculus and smear layer from the root surface and allows for particular removal of sulcular or pocket epithelium, laser-treated root surface may enable more suitable environment for increased connective tissue attachment and may also enhance periodontal healing.[10,13] This positive finding can

indicate that Er, Cr: YSGG laser can be used as an adjunct to SRP in periodontal treatment.

Recent studies have shown that the laser radiation affects the production of cytokines and may modulate the oral inflammatory response.[31] In this study, the GCFvol, IL-1 β, and IL-6 levels in both SRP and SRP + laser groups showed statistically important decreases at the times measured compared to the baseline, without showing substantial differences among the groups. There was a positive correlation between the levels of IL-1 β, IL-6, GCFvol, and clinical parameters (PI, GI, and BOP). GCF has been presented as a potential diagnostic value to assess the disease activity and periodontal treatment efficacy.[14] The findings of this study in consistent with the previous studies indicated that the GCF levels of proinflammatory cytokines are higher in sites of inflammation, and reductions were seen after periodontal treatment.[15,32-34] Offenbacher *et al*.[15] explained that patients with deep pocket depths and more severe BOP had increased GCF IL-1β and IL-6 levels. Miyazaki *et al*.[32] analyzed the immunological effects and made a comparison between Nd: YAG laser monotherapy and ultrasonic scaling for nonsurgical treatment of patients with chronic periodontitis and reported that the intergroup analysis did not prove any statistical importance, even though the Nd: YAG group tended to achieve a reduction in IL-1 β, comparatively. Saglam *et al*.[33] conducted a randomized, parallel, and controlled clinical trial to investigate the biochemical and clinical efficacy of diode laser as a complementary treatment to SRP in patients with chronic periodontitis and reported that the amounts of IL-1 β and IL-6 decreased ($P < 0.05$) following the treatments in both test group and control group ($P < 0.05$) with no statistically significant differences between groups. Eltas and Orbak[34] compared the effects of Nd: YAG laser + SRP and SRP alone in chronic periodontitis patients by determining the clinical indices and levels of IL-1 β and matrix metalloproteinase-8 (MMP-8) in GCF before and after the treatment and found out that even though IL-1 β and MMP-8 levels in GCF following the treatment were reduced in the SRP + Nd:YAG laser (NDL) compared to the SRP, the differences were not statistically considerable ($P > 0.05$). On the other hand, Qadri *et al*.[31] reported that levels of IL-1 β and MMP-8 substantially decreased by Nd: YAG laser treatment, indicating that laser type could play a key role on the results of the treatment. Gómez *et al*.[35] presented a randomized clinical study to determine the clinical, microbiological, and anti-inflammatory efficacy of Nd: YAG laser in periodontal treatment as a complementary to SRP and found out that statistically significant differences for clinical or microbiological variables could not be observed between the treatments of SRP and SRP + Nd: YAG. On the other hand, the IL-1 β levels in GCF were substantially decreased following the SRP + Nd: YAG treatment.

T-cells have a significant key role in the regulatory immune response, and Gershon and Kondo[36] demonstrated the potential suppressive activity of T-cells for the first time. The authors indicated that as well as enhancing the inflammatory response, T-cells also suppress them. Previously, it has been established that Treg expression is elevated by stimulation with *Porphyromonas gingivalis* antigens in periodontitis patients.[37] Recent studies indicated that the number of Treg cells was significantly superior in chronic periodontitis lesions compared to gingivitis lesions.[38,39] Cardoso *et al*.[38] indicated that Tregs accumulate inside the periodontitis patients' gingiva and limit the effector immune responses and promote pathogen survival, which result in maintaining the chronicity of the disease. Furthermore, it has been reported that Treg infiltration could indicate an attempt to take tissue destruction under control but could also reflect a destructive role in periodontal disease.[39]

IL-35, the newest part of IL-12 cytokine family, is produced by Treg cells and also from smooth muscle cells, microvascular endothelial cells, and monocytes.[20-23] It has been shown that IL-35 appears to play an immunomodulatory role in an extensive variety of disease circumstances.[23,24] In an *in vivo* study, recombinant IL-35 injections protected laboratory mice against rheumatoid arthritis which is a chronic inflammatory disease, as is periodontitis.[24]

In the present study, the GCFvol and IL-35 levels in SRP and SRP + laser groups decreased at all time points (1, 3, and 6 months) following the treatment, but reductions were statistically significant at 6 months compared to baseline. Broadly, IL-1 β/IL-35 ratio changed from 3/1 to 1/1 throughout the study. This finding may be explained by the rearrangement of cytokine balance from disease to health. According to our literature review, although very few papers were published regarding biocompatibility of IL-35 in gingival tissues and GCF, there is no published study comparing the effects of either Er, Cr: YSGG laser or SRP treatments on GCF IL-35 levels. Hence, we cannot compare our results with other studies, but our finding is in consistent with previous two studies. Kalburgi *et al*.,[25] Jin *et al*.,[40] and Kalburgi *et al*.[25] demonstrated the expression of IL-35 mRNA in gingival tissues of chronic periodontitis, aggressive periodontitis, and healthy tissues and proved that IL-35 is related to the pathogenesis of periodontitis. Jin *et al*.[40] indicated that IL-35 expression increases with CP development, which may help attenuate the process of chronic periodontitis.

Conclusions

As part of the present study results, as GCF IL-1 β/IL-35 ratio changed significantly from disease to health, we can suggest that IL-35 may be associated within the pathogenesis of periodontitis and that Er, Cr: YSGG laser can be used as an adjunct to SRP in periodontal treatment. Further longitudinal clinical, microbiological, and biochemical studies are required for the evaluation of the exact role of host mediated cytokine network in the pathogenesis of periodontal disease. In the future, identification of patients having high susceptibility sites for periodontal disease activities by diagnostic biochemical markers will possibly provide patient site-specific treatment methods.

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Conflicts of interest

There are no conflicts of interest.

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