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Melike Camgoz[1], Nilsun Bagis[2], Elif Unsal[2]

Adjunctive Systemic Azithromycin with Nonsurgical Periodontal Treatment: Effects on Clinical Parameters in Smokers with Periodontitis

Pomoćna sistemska primjena azitromicina uz nekirurško parodontološko liječenje: učinci na kliničke parametre kod pušača s parodontitisom

[1] Gazi University, Faculty of Dentistry, Ankara, Turkey.
Stomatološki fakultet Sveučilišta Gazi, Ankara, Turska
[2] Ankara University, Faculty of Dentistry, Department of Periodontology, Ankara, Turkey.
Zavod za parodontologiju Stomatološkog fakulteta Sveučilišta Ankara, Ankara, Turska

Abstract
Objectives: Smokers with periodontitis are therapeutically challenging. Azithromycin (AZM) may be used as an adjunct to periodontal treatment. The aim of this randomized, double-blind, controlled clinical study was to determine the effect of azithromycin in shallow, moderate, and deep pocket depths in smokers when combined with non-surgical periodontal treatment. **Material and methods:** Forty-nine patients who smoked at least 20 cigarettes per day for more than 5 years were included in the study; however only 40 completed it. The number of teeth, plaque index (PI), gingival index (GI), PPD, CAL, bleeding on probing (BOP) and gingival recession were recorded at baseline and months 1, 3 and 6. The pocket depths (PD) were grouped as shallow, moderate, and deep. Twenty-four patients assigned to the AZM+ (test) group received AZM (500 mg tablets) once a day for 3 days, beginning on the first day of SRP. **Results:** The decline in the total number of pockets in all groups was statistically significant from baseline to 1st, baseline to 3rd, baseline to 6th; and from 1st to 3rd and 1st to 6th months. There was a statistically significant increase in the number of shallow pockets between baseline and 3rd, baseline and 6th; and 1st and 6th months (p=0.000) for both groups. **Conclusion:** Antibiotic administration significantly increased the number of shallow pockets at all time points. However, larger scale controlled clinical studies are needed to verify the efficiency of AZM in smoker periodontitis patients.

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Address for correspondence
Dr. Melike CAMGOZ
Gazi Universitesi Dis Hekimligi Fakultesi
Ogretim Uyeleri (VIP) Klinigi
Emek Mah, Bişkek Cd. 1. Sokak D:No:4
06490 Çankaya
Ankara / TURKEY
Phone: +90 312 2034210
mlkozcan@yahoo.com

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Melike Camgoz 0000-0001-5241-019X
Nilsun Bagis 0000-0003-4301-8502
Elif Unsal 0000-0002-7843-6088

Introduction

Periodontitis is a destructive type of periodontal disease which affects the periodontium with prevalence 20-50% globally (1). It is a result of an interaction between bacterial microbiota and host response (1, 2). The host response is important (3) and the objective of periodontal therapy is to reduce the bacterial load. It has been proven that mechanical therapy is efficient in the long term (4, 5). Smoker periodontitis patients may not respond to therapy (6, 7). Smoking is among major risk agents of periodontitis (8), and it can decrease the effect of treatment. Studies demonstrated less clinical attachment gain in smokers (9-12).

The systemic antimicrobial usage in combination with scaling and root planning (SRP) has superior results (5, 13-

Uvod

Parodontitis je destruktivna parodontna bolest koja zahvaća parodont s prevalencijom od 20 do 50 % na globalnoj razini (1). To je rezultat interakcije između bakterijske mikrobiote i odgovora domaćinu (1, 2). Odgovor domaćina je važan (3), a cilj je parodontološke terapije smanjiti bakterijsko opterećenje. Dokazano je da je mehanička terapija dugoročno učinkovita (4, 5). Pacijenti pušači s parodontitisom možda neće odgovoriti na terapiju (6, 7). Pušenje je jedan od glavnih uzročnika rizika od parodontitisa (8) i može smanjiti učinak liječenja. Istraživanja su kod pušača pokazala manji klinički porast adherencije (9 – 12).

Sistemska primjena antimikrobnih lijekova u kombinaciji s čišćenjem kamenca i struganjem korijena (SRP) omoguću-

15) with significant improvements in non-smokers (16-17) and supplementary clinical advantages in smokers with chronic periodontitis (CP) (18-20). It has been reported that some antibiotics might have superior effects in clinical trials. However, the results regarding azithromycin (AZM) were shown to be contradictory. The use of AZM in chronic periodontitis was found appropriate; but no better affect was observed in aggressive periodontitis patients (21).

Azithromycin (AZM), a macrolide with captivating curative effects, has a better oral absorption and could be used as an adjunct to periodontal treatment (1, 22). It is effective against many infections with a broad range of effects on Gram-negative and Gram-positive periodontopathogens (23, 24). It slows down the microbial infection, enhances periodontal healing by depressing detrimental pathogens, thus improving immune response (25). In addition to these pharmacological properties, AZM is favorable due to the following; long half-life resulting in a short dose regimen, better patient compliance, rare side effects, anti-inflammatory effects as well as bacteriostatic activity, and residence and/or migration of leukocytes and fibroblasts into the periodontal tissue as a result of prolonged release (26).

The objective of this randomized, controlled, single-blind clinical trial was to determine the effect of azithromycin combined with non-surgical periodontal treatment in shallow, moderate, and deep probing pocket depths.

Material and methods

This study was designed as a single center, randomized parallel study of AZM in patients with moderate to advanced chronic periodontitis (according to the new classification: Stage III or IV, Grade B generalized periodontitis) who are also smokers (27,28). The study was performed during 2015-2016; therefore the patients were diagnosed depending on the 1999 classification of the American Academy of Periodontology (27). Participants were randomly chosen from patients who applied to Ankara University, Faculty of Dentistry, Department of Periodontology, for periodontal treatment or for periodontal screening. The participants were informed about the study and written informed consents were obtained as required by the Declaration of Helsinki. The study was evaluated and approved by the Ethics Committee for the use of human subjects in research (Ref.no: 36290600/10/6).

Patients aged 30 years or older who were heavy smokers (≥20 cigarettes per day) for over 5 years were chosen for the study, and the periodontitis inclusion criteria were as follows: 1) a minimum of 16 teeth; 2) at least 8 sites with a probing pocket depth (PPD) of 6 mm; and 3) at least 4 sites with clinical attachment level (CAL) of 5 mm are present, distributed in at least two sets (29).

Patients with a history of systemic antibiotic use in past 3 months, non-surgical periodontal therapy in past 6 months, surgical periodontal therapy within the last year, fewer than 16 teeth, current use of phenytoin, calcium channel blockers, or cyclosporine, or pregnancy or diabetes mellitus were excluded. Also, patients with any allergy to medications used in the study were excluded as well. Data regarding patients'

je superiorne rezultate (5, 13 – 15) sa značajnim poboljšanjima kod nepušača (16 – 17) i dodatnim kliničkim prednostima kod onih s kroničnim parodontitisom (CP) (18 – 20). Zabilježeno je da bi se nekim antibioticima mogli postići bolji učinci u kliničkim istraživanjima. Međutim, rezultati koji se odnose na azitromicin (AZM) pokazali su se kontradiktornima. Primjena AZM-a u slučaju kroničnog parodontitisa pokazala se prikladnom, no bolji učinak nije primijećen kod agresivnog parodontitisa (21).

Azitromicin (AZM), makrolid zadivljujućeg ljekovitog djelovanja, ima bolju oralnu apsorpciju i mogao bi se koristiti kao dodatak parodontološkoj terapiji (1, 22). Djelotvoran je kad je riječ o mnogim infekcijama i ima široki raspon učinaka na gram-negativne i gram-pozitivne parodontopatogene (23, 24). Usporava mikrobnu infekciju, pospješuje parodontno cijeljenje potiskujući štetne patogene i tako poboljšava imunosni odgovor (25). Uz ta farmakološka svojstava, AZM je povoljan zato što ima dugi poluvijek što rezultira kratkim režimom doziranja, pacijenti bolje surađuju, nuspojave su rijetke, a protuupalni učinci i bakteriostatsko djelovanje te zadržavanje i/ili migracija leukocita i fibroblasta u parodontno tkivo rezultat su produljenog oslobađanja (26).

Cilj ovoga randomiziranog, kontroliranog, jednostruko slijepog kliničkog istraživanja bio je utvrditi učinak azitromicina u kombinaciji s nekirurškom parodontološkom terapijom plitkih, umjerenih i dubokih džepova.

Materijal i metode

Ovo je istraživanje osmišljeno kao unicentrično, randomizirano paralelno istraživanje o primjeni AZM-a kod pacijenata s umjerenim do napredovalim kroničnim parodontitisom (prema novoj klasifikaciji: stupanj III ili IV, ocjena B generalizirani parodontitis) koji su ujedno i pušači (27, 28). Istraživanje je provedeno tijekom 2015. i 2016. godine i zato je pacijentima postavljena dijagnoza prema klasifikaciji Američke akademije za parodontologiju iz 1999. (27). Sudionici su nasumično odabrani među pacijentima koji su se prijavili za parodontološko liječenje ili parodontološki probir na Stomatološkom fakultetu Sveučilišta u Ankari i u Zavodu za paradontologiju. Sudionici su obaviješteni o istraživanju i potpisali su informirane pristanke prema Helsinškoj deklaraciji. Istraživanje je odobrilo i ocijenilo Etičko povjerenstvo za korištenje ljudskih subjekata u istraživanjima (ref. br.: 36290600/10/6).

Za istraživanje odabrani su pacijenti teški pušači dulje od pet godina u dobi od 30 godina ili stariji (≥ 20 cigareta na dan), a kriteriji za uključivanje bili su sljedeći: 1) najmanje 16 zuba; 2) najmanje osam mjesta s dubinom sondiranja džepova (PPD) od 6 mm, 3) najmanje četiri mjesta s kliničkom razinom pričvrstka (CAL) od 5 mm raspoređena u najmanje dva skupa (29).

Isključeni su pacijenti s anamnezom sistemske primjene antibiotika u posljednja tri mjeseca, zatim oni kod kojih je primijenjena nekirurška parodontološka terapija u posljednjih šest mjeseci, kirurška parodontološka terapija u posljednjih godinu dana i manje od 16 zuba, ili zbog trenutačne upotrebe fenitoina, blokatora kalcijevih kanala ili ciklospo-

smoking status, sex and age were recorded at baseline.

Forty-nine patients qualified for the study, but only 40 completed it. All clinical evaluations of the participants were performed by one trained and calibrated single-blinded examiner (N.B.) at first appointment. Calibration prior to the study was carried out with five volunteers. Reproducibility was defined by calculation of the percentage of the evaluated sites where the scores were exactly the same, or in an accuracy of 1 mm. The estimation of the mean difference in the scores (with 85% accuracy) between two examinations showed that there were not any systematic preconceptions in measurements. Charting, including number of teeth, plaque index (PI) (30), gingival index (GI) (31), PPD, CAL and bleeding on probing (BOP) and gingival recession was performed at baseline, months 1, 3 and 6. In order to measure probing pocket depth and CAL a Williams' probe *('O' Probe with Williams, University of Michigan*) was used at 4 sites around each tooth (lingual, disto-buccal, mid-buccal, and mesio-buccal). All measurements were made by the same periodontologist (N.B.). The mean values for whole mouth PI, GI, PPD, CAL and the number of sites with BOP were divided by the total number of sites per mouth and multiplied by 100 for each subject. The probing pocket depths were grouped as shallow (1-2 mm loss in clinical attachment), moderate (3-4 mm loss in clinical attachment), and deep (clinical attachment loss ≥5 mm).

At baseline, all participants received oral hygiene instructions consisting of tooth brushing and interdental cleaning for home care. An antimicrobial mouthwash was not administered. They received SRP in the course of two appointments at which hand instruments (*Biotech Instruments Inch., Winooski, WT, USA*) and an ultrasonic scaler (*Varios 570 NSK, Japan*) were used under local anesthesia. Treatments were performed by a 10-year-experienced periodontologist (M.C.) and completed within 7 days. At the end of the first SRP application, patients were randomly appointed to one of the two study groups. Another study coordinator (E.U.), who was blind to the applied treatment, pulled test or control designations out of a bag to determine groups. The examiner and the clinician who administered the treatment were both blind to the patient's identity. Twenty-four patients assigned to the AZM+ (test) group received one tablet of AZM (500 mg) a day for 3 consecutive days, starting on the first day of SRP. Tablets were taken two hours after or an hour before the meal. The highest dose with the active ingredient azithromycin available on the market in Turkey is 500 mg tablets. Therefore, this application was preferred. The 25 patients in the control group (AZM-) did not receive any drugs. All measurements at all-time points were performed by the same examiner.

Statistical Analysis

Minimum, maximum, median, and mean standard deviation values for constant data; and percentile values for dashed data are represented in descriptive statistics. The data related with sex and ages were analyzed using the chi square test and T-test respectively in each group. The relevance of clinical measurements was tested. The state of normal distribu-

rina te trudnoće ili dijabetesa melitusa. Također su isključeni pacijenti s bilo kakvom alergijom na lijekove korištene u istraživanju. Podatci o statusu pušenja, spolu i dobi pacijenata zabilježeni su na početku.

U istraživanje je uključeno 49 pacijenata, ali samo 40 sudjelovalo je do kraja. Sve kliničke procjene sudionika obavio je na prvom pregledu jedan uvježbani i kalibrirani jednostruko slijepi ispitivač (N. B.). Kalibracija prije istraživanja provedena je s pet dobrovoljaca. Ponovljivost je definirana izračunom postotka procijenjenih mjesta gdje su rezultati bili potpuno jednaki, ili u točnosti od 1 mm. Procjena srednje razlike u rezultatima (s 85 % točnosti) između dvaju mjerenja pokazala je da nema sustavne pristranosti u mjerenjima. Grafikon, uključujući broj zuba, indeks plaka (PI) (30), gingivni indeks (GI) (31), PPD, CAL, krvarenje pri sondiranju (BOP) i recesiju gingive, provedeno je na početku tretmana te poslije jednoga, tri i šest mjeseci. Kako bi se izmjerili dubina džepova i CAL, korištena je Williamsova sonda ('O' sonda prema Williamsu, Sveučilište u Michiganu) na četirima mjestima oko svakog zuba (lingvalno, distobukalno, mediobukalno i meziobukalno). Sva mjerenja obavio je isti parodontolog (N. B.). Srednje vrijednosti za PI, GI, PPD, CAL i broj mjesta s BOP-om podijeljene su s ukupnim brojem mjesta u ustima i pomnožene sa 100 za svaki subjekt. Dubine džepova grupirane su kao plitke (gubitak kliničkoga pričvrstka 1 – 2 mm), umjerene (gubitak kliničkoga pričvrstka 3 – 4 mm) i duboke (gubitak kliničkoga pričvrstka ≥ 5 mm).

Na početku su svi sudionici dobili upute o oralnoj higijeni koja se sastojala od četkanja zuba i interdentalnog čišćenja kod kuće. Nije primijenjena antimikrobna tekućina za ispiranje usta. Proveden je SRP tijekom dvaju pregleda, pri čemu su u lokalnoj anesteziji korišteni ručni instrumenti (Biotech Instruments Inch., Winooski, WT, SAD) i ultrazvučni strugač (Varios 570 NSK, Japan). Postupak je obavio parodontolog (M. C.) s 10-godišnjim iskustvom i završen je u roku od sedam dana. Nakon prvoga SRP-a, pacijenti su nasumično raspoređeni u jednu od dviju ispitivanih skupina. Drugi koordinator istraživanja (E. U.), koji nije bio obaviješten o primijenjenoj terapiji, izvukao je oznake „test" ili „kontrola" iz vrećice kako bi odredio skupine. I ispitivač i kliničar koji je provodio terapiju nisu znali identitet pacijenata. Njih 24 raspoređeno je u skupinu AZM+ (testna) i dobivali su jednu tabletu AZM-a (500 mg) na dan tijekom tri uzastopna dana, počevši od prvoga dana SRP-a. Tablete su uzimali dva sata poslije obroka ili sat prije. Najveća doza s aktivnim sastojkom azitromicinom dostupna na tržištu u Turskoj jest tableta od 500 mg. Zato je bila poželjna takva aplikacija. U kontrolnoj skupini (AZM-) od 25 pacijenata nitko nije dobivao nikakve lijekove. Sva mjerenja u svim vremenskim točkama obavio je isti ispitivač.

Statistička analiza

Minimalne i maksimalne vrijednosti, medijan i srednje vrijednosti standardne devijacije za konstantne podatke i postotne vrijednosti za crtkane podatke predstavljene su u deskriptivnoj statistici. Podatci koji se odnose na spol i dob analizirani su s pomoću Hi-kvadrat i T-testa u svakoj skupini. Ispitana je relevantnost kliničkih mjerenja. Stanje normal-

tion was evaluated with Repeated Measures Variant Analysis, whereas Friedman Test was used when normal distribution was not present. The power analysis revealed a probability of less than 0.05 with 85% power for 20 patients in per group. Data were analyzed using the SPSS 11.5 (SPSS. Inc. Chicago, IL, USA) package, and the statistical significance was considered p<0.05.

Results

The mean age of the study group was 47.57±5.91 (range: 36-58 years). There were no statistically significant differences between test and control groups regarding age and sex (Table 1) (p>0.05). Daily cigarette consumption was similar in both groups.

Azithromycin was well tolerated in both groups and no adverse effects were observed. The interaction term (GxT) was not statistically significant between both groups for PI (GxT; F (2.292, 87.095) = 1.152, p=0.326). The PI values at baseline, 1st month, 3rd month, and 6th month were similar for both groups (Table 2). The GI values were lower in AZM+ group compared to AZM- group at all time periods, and this difference was statistically significant (GxT; F (1.38) = 48.810, p=0.000, p<0.001) (Table 2).

The decrease in total number of pockets in test group (AZM+) was statistically significant from baseline to 1st, baseline to 3rd, baseline to 6th; and from 1st to 3rd and 1st to 6th months. A statistically significant increase in the number of shallow pockets between baseline and 3rd, baseline and 6th; and 1st and 6th months (p=0.000) was observed. The decrease in total number of pockets in AZM- group was statistically significant from baseline to 1st, baseline to 3rd, baseline to 6th; and from 1st to 6th months. There was also a statistically significant increase in the number of shallow pockets between

ne distribucije procijenjeno je analizom varijanti ponovljenih mjerenja, a Friedmanov test korišten je kada distribucija nije bila normalna. Analiza snage otkrila je vjerojatnost manju od 0,05 s 85 % snage za 20 pacijenata u skupini. Podatci su analizirani s pomoću paketa SPSS 11.5 (SPSS. Inc. Chicago, IL, SAD), a statistička značajnost bila je p < 0,05.

Rezultati

Prosječna dob u ispitivanoj skupini bila je 47,57 ± 5,91 (raspon: 36 – 58 godina). Nije bilo statistički značajnih razlika između ispitne i kontrolne skupine s obzirom na dob i spol (tablica 1.) (p > 0,05). Dnevna konzumacija cigareta u objema skupinama bila je slična.

Azitromicin su obje skupine dobro podnosile i nisu uočene nuspojave. Interakcija (GxT) između dviju skupina nije bila statistički značajna za PI [GxT; F (2,292, 87,095) = 1,152, p=0,326]. PI vrijednosti na početku te poslije prvoga, trećeg i šestog mjeseca bile su slične za obje skupine (tablica 2.). GI vrijednosti bile su niže u skupini AZM+ u odnosu prema skupini AZM- u svim vremenskim razdobljima, a ta je razlika bila statistički značajna [GxT; F (1,38) = 48,810, p = 0,000, p < 0,001] (tablica 2.).

Smanjenje ukupnog broja džepova u ispitivanoj skupini (AZM+) bilo je statistički značajno od početka tretmana do prvog mjeseca, od početka tretmana do trećeg mjeseca, od početka tretmana do šestog mjeseca te od prvog do trećeg i prvog do šestog. mjeseca. Statistički značajno povećanje broja plitkih džepova zabilježeno je između početne vrijednosti i trećeg mjeseca, početne vrijednosti i šestog mjeseci te prvog i šestog mjeseca (p = 0,000). Smanjenje ukupnoga broja džepova u skupini AZM- bilo je statistički značajno od početne vrijednosti do prvog mjeseca i od početne vrijednosti do tre-

Table 1 Distribution of age and sex.
Tablica 1. Distribucija prema dobi i spolu

		AZM+ (n=21)		AZM- (n=19)		p
Age • Dob	Mean±SD • Sredina±SD	46.52±5.58		48.74±6.19		0.242*
Gender • Spol		Female • Ženski	Male • Muški	Female • Ženski	Male • Muški	0.301**
	n	10	11	6	13	
	%	47,6	52,4	31,6	68,4	

SD: Standard deviation • standardna devijacija, *T-test, **Chi-square test • Hi-kvadrat test

Table 2 PI and GI values at evaluation periods (0-1-3-6 months)
Tablica 2. PI i GI vrijednosti u evaluacijskim razdobljima (0-1-3-6 mjeseci)

		Time • Vrijeme (T)				p
		Baseline • Početak	1 month • 1 mjesec	3 months • 3 mjeseca	6 months • 6 mjeseci	
	Group • Skupina	Mean±SD • Sredina±SD	Mean±SD • Sredina±SD	Mean±SD • Sredina±SD	Mean±SD • Sredina±SD	
PI	Azm +	1.92± 0.51	0.53± 0.26	0.44± 0.21	0.47± 0.20	0.000
	Azm -	2.09± 0.24	0.55± 0.23	0.45± 0.17	0.62± 0.16	<0.001
GI	Azm +	0.53±0.26	0.12±0.09	0.08±0.03	0.20±0.09	0.000
	Azm -	0.60±0.17	0.29±0.12	0.44±0.23	0.51±0.19	<0.001

T: Time (Baseline, 1st month, 3rd month, 6th month), GxT: Interaction Term • Vrijeme (početak, 1. mjesec, 3. mjesec, 6. mjesec), GxT: pojam interakcije

Table 3 Comparison of PPD measurements at 0,1,3 and 6 months separately in both groups.
Tablica 3. Usporedba mjerenja PPD-a u 0., 1., 3. i 6. mjesecu zasebno u objema skupinama

	AZM +		AZM -	
	Mean ± SD • Sredina ± SD	Median (Min-Max) • Medijan (min.-maks.)	Mean ± SD • Sredina ± SD	Median (Min-Max) • Medijan (min.-maks.)
PD Baseline • PD početni	4.23±0.45	4.12 (3.49-5.16	4.25±0.46	4.23 (3.32-5.12)
PD 1st month • PD 1. mjesec	2.37±0.60	2.09 (1.85-3.96)	3.16±0.51	3.02 (2.26-4.08)
PD 3rd month • PD 3. mjesec	1.89±0.43	1.85 (1.44-2.98)	2.87±0.47	2.99 (1.94-3.65)
PD 6th month • PD 6. mjesec	1.74±0.42	1.56 (1.33-3.03)	2.67±0.33	2.66 (1.96-3.16)
p*	0.000		0.000	
PD Shall Baseline	48.90±15.26	55 (23-71)	55.31±12.21	59 (24-71)
PD 1st month	73.48±9.75	76(54-87)	70.59±10.53	73 (40-83)
PD 3rd month	80.05±8.92	83 (64-91)	76.68±7.02	78 (58-86)
PD 6th month	88.62±9.15	89 (67-101)	81.47±6.23	83 (68-91)
p*	0.000		0.000	
PD MDR Baseline	44.86±13.83	44 (14-63)	39.74±11.64	34 (21-60)
PD MDR 1st month	30.62±8.55	30 (15-46)	28.47±9.87	26 (16-47)
PD MDR 3rd month	25.48±7.93	22 (14-41)	23.53±5.86	23 (16-36)
PD MDR 6th month	17.05±8.46	15 (5-37)	19.58±6.83	19 (8-32)
p*	0.000		0.000	
PD DEEP Baseline	13.09±3.82	12 (9-23)	12.95±3.58	13 (8-24)
PD DEEP 1st month	2.76±1.48	2 (1-8)	8.95±3.61	8 (5-21)
PD DEEP 3rd month	1.33±1.15	1 (0-5)	7.79±3.55	8 (3-19)
PD DEEP 6th month	1.19±0.98	1 (0-4)	6.95±2.99	6 (3-16)
p*	0.000		0.000	
AL Baseline	4.76±0.84	4.24 (3.94-6.69)	4.76±0.95	4.36 (3.33-6.85)
AL 1st month	2.49±0.61	2.22 (1.59-3.98)	3.48±0.81	3.21 (2.26-5.01)
AL 3rd month	2.16±0.52	2.06 (1.42-3.19)	3.08±0.74	3.01(1.99-4.86)
AL 6th month	2.13±0.60	2.11 (1.36-3.98)	2.85±0.58	2.87 (1.96-4.19)

SD: Standard Deviation, Min: Minimum, Max: Maximum, *Friedman Test • SD: standardna devijacija, min.: minimum, maks.: maksimum, * Friedmanov test

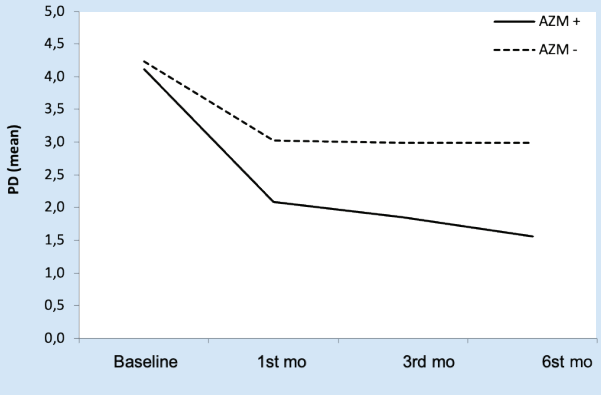

Figure 1 PD vs time in AZM+ and AZM– groups
Slika 1. PD nasuprot vremenu u skupinama AZM+ i AZM–

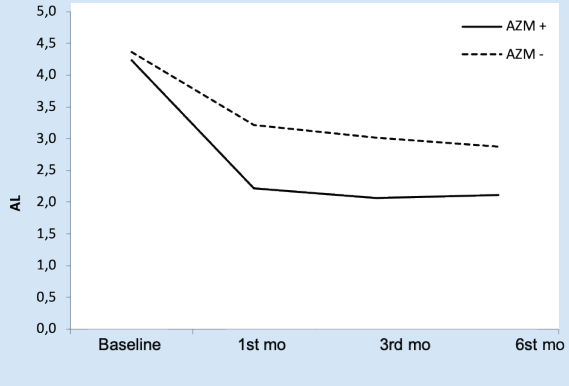

Figure 2 CAL vs time in AZM+ and AZM– groups
Slika 2. CAL nasuprot vremenu u skupina AZM+ i AZM–

baseline and third months, baseline and sixth months, and the first and sixth months (p=0.000) for this group (Table 3).

Table 4 shows the amounts of rise in the number of shallow pockets, where positive values indicate a greater increase, and negative values indicate a lower increase.

The difference in overall (total number of) pockets between baseline and first month, and baseline and third month, was statistically significant (p<0.001). The decrease

ćeg mjeseca, te od početne vrijednosti do šestog mjeseca i od prvoga do šestog mjeseca. Također se statistički značajno povećao broj plitkih džepova između početne vrijednosti i trećeg mjeseca, početne vrijednosti i šestog mjeseca te prvoga i šestog mjeseca (p = 0,000) za ovu skupinu (tablica 3.).

U tablici 4. prikazani su iznosi porasta broja plitkih džepova, pri čemu pozitivne vrijednosti upućuju na veći porast, a negativne na manji porast.

in the AZM+ group was greater, indicating that a greater number of pockets became shallower in this group (Figure 1). The change in overall pocket depth and/or shallow, moderate, and deep pockets between months 1 and 3, 1 and 6, and 3 and 6 was not statistically different for either group ($p<0.05$). The change in shallow pockets was statistically significant between AZM+ and AZM- groups from baseline to 1st, baseline to 3rd, and baseline to 6th months ($p<0.01$).

The reduction in pocket depth was greater in the AZM+ group (Table 4). The difference in deep pockets between the AZM+ and AZM- groups from baseline to first, third, and sixth months was also statistically significant ($p<0.01$). In this regard, the decrease was greater in the AZM+ group (Tables 3-4). The difference in attachment levels was statistically significant between both groups from baseline to 1st, 3rd, and 6th months (Figure 2). The AZM+ group showed greater improvement in periodontal sites over time as measured by CAL value gain.

Razlika u ukupnom broju džepova između početne vrijednosti i prvog mjeseca te početne vrijednosti i trećeg mjeseca bila je statistički značajna ($p < 0,001$). Smanjenje u skupini AZM+ bilo je veće, što upućuje na to da je u toj skupini veći broj džepova postao plići (slika 1.). Promjena ukupne dubine plitkih, umjerenih i dubokih džepova između prvog i trećeg mjeseca, prvog i šestog mjeseca te trećeg i šestog mjeseca nije bila statistički različita ni za jednu skupinu ($p < 0,05$). Promjena plitkih džepova bila je statistički značajna između skupina AZM+ i AZM- od početne vrijednosti do prvog mjeseca, od početne vrijednosti do trećeg mjeseca i od početne vrijednosti do šestog mjeseca ($p < 0,01$).

Smanjenje dubine džepova bilo je veće u skupini AZM+ (tablica 4.). Razlika u dubokim džepovima između skupina AZM+ i AZM- od početne vrijednosti do prvoga, trećeg i šestog mjeseca također je bila statistički značajna ($p < 0,01$). S tim u vezi, smanjenje je bilo veće u skupini AZM+ (tablice 3. i 4.). Razlika u razinama pričvrstka bila je statistički značajna između obiju skupina od početne vrijednosti do prvoga, tre-

Table 4 Comparison of changes (difference) between time points in AZM + and AZM – groups.
Tablica 4. Usporedba promjena (razlika) između vremenskih točaka u skupinama AZM+ i AZM –

	AZM +		AZM -		
	Mean ± SD • Sredina ± SD	**Median (Min-Max) • Medijan (min.-maks.)**	**Mean ± SD • Sredina ± SD**	**Median (Min-Max) • Medijan (min.-maks.)**	**p***
PD Baseline-1st month	-1.85±0.41	-1.9 (-2.90- -1.14)	-1.10±0.41	-1.04 (-1.89- -0.22)	0.000
PD Baseline-3rd month	-2.34±0.36	-2.39(-3.02- -1.61)	-1.38±0.55	-1.34(-2.62- -0.64)	0.000
PD Baseline-6th month	-2.50±0.40	-2.48(-3.45- -1.89)	-1.58±0.50	-1.65(-2.60- -0.77)	0.000
PD 1st month-3rd month	-0.48±0.33	-0.42(-1.12- -0.02)	-2.87±0.44	-0.10(-1.19- -0.40)	0.054
PD 1st month-6th month	-0.63±0.41	-0.55(-1.57- -0.05)	-0.49±0.48	-0.31(-1.67- 0.09)	0.169
PD 3rd month-6th month	-0.16±0.18	-0.09(-0.48- 0.06)	-0.20±0.41	-0.20(-1.22- 0.54)	1.000
PD SHALL Baseline-1st month	24.57±9.69	22 (8-46)	15.26±7.99	15 (6-39)	0.001
PD SHALL Baseline-3rd month	31.14±10.32	29 (14-52)	21.37±8.56	21 (7-37)	0.003
PD SHALL Baseline-6th month	39.71±10.95	41 (20-63)	26.16±10.08	25 (11-49)	0.000
PD SHALL 1st-3rd month	6.57±3.28	6 (1-15)	6.10±4.99	5 (-2-18)	0.376
PD SHALL 1st-6th month	15.14±5.99	14 (4-31)	10.89±6.24	9 (2-28)	0.013
PDSHALL 3rd-6th month	8.57±4.31	9 (1-16)	4.79±4.87	5 (-8-12)	0.019
PD MDR Baseline-1st month	-14.24±10.53	-14 (-39- 3)	-11.26±7.57	-11 (-34- -2)	0.247
PD MDR Baseline-3rd month	-19.38±10.74	-18 (-43- 0)	-16.21±8.80	-15 (-33- -4)	0.294
PD MDR Baseline-6th month	-27.81±11.24	-25 (-49- -9)	-20.16±9.89	-20 (-44 - -5)	0.022
PD MDR 1st-3rd month	-5.14±3.35	-5 (-14- -1)	-4.94±5.13	-3 (-17- 2)	0.503
PD MDR 1st-6th month	-13.57±6.33	-13 (-29- -2)	-8.89±5.80	-8 (-23- 0)	0.016
PD MDR 3rd-6th month	-8.43±4.25	-9 (-15- -1)	-3.95±4.65	-5 (-12- 9)	0.004
PD DEEP Baseline-1st month	-10.33±3.09	-10 (-17- -6)	-4.0±1.29	-4 (-6- -1)	0.000
PD DEEP Baseline-3rd month	-11.76±3.31	-11 (-19- -8)	-5.16±1.80	-5 (-8- -1)	0.000
PD DEEP Baseline-6th month	-11.90±3.40	-11 (-19- -8)	-6.0±1.70	-6 (-9- -2)	0.000
PD DEEP 1st-3rd month	-1.43±1.12	-2 (-4- 0)	-1.16±1.12	-1 (-3- 1)	0.520
PD DEEP 1st-6th month	-1.57±1.16	-2 (-4- 0)	-2.0±1.25	-2 (-5- 0)	0.320
PD DEEP 3rd-6th month	-0.14±0.36	0 (-1- 0)	-0.84±0.96	-1 (-3- 0)	0.022
AL Baseline-1st month	-2.27±0.72	-2.16 (-3.8- -0.14)	-1.28±0.56	-1.14 (-2.77- -0.14)	0.000
AL Baseline-3rd month	-2.59±0.72	-2.26(-4.30- -1.71)	-1.68±0.77	-1.56(-2.98- -0.29)	0.000
AL Baseline-6th month	-2.63±0.77	-2.40(-4.35- -1.26)	-1.92±0.67	-1.88(-3.31- -0.93)	0.004
AL 1st month-3rd month	-0.36±0.34	-0.32(-1.10- 0.07)	-0.40±0.58	-0.35(-1.37- 0.84)	0.728
AL 1st month-6th month	-0.36±0.34	-0.30(-1.11- 0)	-0.64±0.65	-0.49(-2.02- 0.53)	0.153

SD: Standard Deviation, Min: Minimum, Max: Maximum • SD: standardna devijacija, min.: minimum, maks.: maksimum

Discussion

Periodontitis and periimplantitis are microbially associated diseases marked by host-mediated inflammation that leads to periodontal attachment loss. A dysbiotic microbiome in the subgingival biofilm in a susceptible host results in the aforementioned conditions (1, 2, 5, 32, 33). Although SRP is the gold standard to manage periodontitis, the mechanical debridement may fail in some specific occasions (1, 4, 6, 32, 34, 35). When, or if, patients have active disease, a specific microbial profile, and/or deep pockets an adjunctive antimicrobial therapy to SRP may become beneficial (13-15, 32, 34). Antibiotics may be used systemically or locally, where the advantage of systemically administered antimicrobials is being able to reach host tissues, especially the entire oral tissues and fluids (32, 34).

Azithromycin, a macrolide called azalide, is used widely as an adjunct to mechanical debridement. Due to its higher resistance to gastric acids, it has a better oral absorption than other antibiotics in the same group (1, 22). It is usually preferred because of its broad spectrum of action, slow release in soft tissues, fast fibroblast and leukocyte absorption, and lesser intake days, which helps with patient compliance (26,36). It significantly enhances the efficacy of nonsurgical periodontal therapy with the reduction in PPD and BOP, and gain in CAL (32, 34). It is effective against several systemic infections as well as oral infections or soft tissue regeneration (24, 37). Therefore, it can be anticipated that the adjunctive AZM therapy would bring out better outcomes. In our study, there was a statistically significant decrease in deep pockets and a statistically significant attachment gain at all-time points in AZM+ group. The GI scores were lower in the AZM+ group compared to the AZM- group throughout the study, and this distinction was also statistically significant. This positive outcome is thought to be a result of a reduction in periodontal pathogens (38).

Periodontal therapy of periodontitis patients who smoke is challenging since their response to the treatment may not be as satisfactory as non-smokers' response to the treatment. The amount of daily consumption may also play a role in periodontal treatment. Adjunctive antimicrobial applications to mechanical debridement have been suggested to intensify the outcomes of therapy. Improved clinical parameters were observed in studies with AZM application in heavy smokers with chronic periodontitis (7). Because our study population was solely comprised of smokers, the effect of AZM in conjunction with SRP was assessed. The reduction in total number of deep pockets was statistically significant from baseline to 1st, 3rd, and 6th months in both groups. The number of shallow pockets increased, indicating that medium and/or deep pockets became shallower, transforming into medium/shallow pockets during both treatment protocols.

The decrease in pocket depths, however, was larger in the AZM+ group than in the AZM- negative group. The reduc-

ćeg i šestog mjeseca (slika 2.). U skupini AZM+ postignuto je veće poboljšanje zahvaćenih mjesta tijekom vremena, mjereno povećanjem CAL vrijednosti.

Rasprava

Parodontitis i periimplantitis bolesti su povezane s mikrobima i obilježava ih upala posredovana domaćinom koja rezultira gubitkom parodontnog pričvrstka. Disbiotski mikrobiom u subgingivnom biofilmu kod osjetljivog domaćina potiče ta navedena stanja (1, 2, 5, 32, 33). Iako je SRP zlatni standard za liječenje parodontitisa, mehaničko čišćenje u nekim specifičnim situacijama može biti neuspješno (1, 4, 6, 32, 34, 35). Kada, ili ako pacijenti imaju aktivnu bolest, specifičan mikrobni profil i/ili duboke džepove, uz SRP može biti korisna dodatna antimikrobna terapija (13 – 15, 32, 34). Antibiotici se mogu primijeniti sustavno ili lokalno, pri čemu je prednost sustavno primijenjenih antimikrobika u tome što mogu doprijeti do tkiva domaćina, posebno do cjelokupnoga oralnog tkiva i tekućina (32, 34).

Azitromicin, makrolid nazvan azalid, naširoko se upotrebljava kao dodatak mehaničkom čišćenju. Zbog veće otpornosti na žučnu kiselinu bolje se oralno apsorbira od ostalih antibiotika iz iste skupine (1, 22). Obično mu se daje prednost zbog širokog spektra djelovanja, sporog otpuštanja u mekim tkivima te brze apsorpcije fibroblasta i leukocita, a liječenje je kraće što pomaže suradnji pacijenata (26, 36). Značajno povećava učinkovitost nekirurške parodontološke terapije sa smanjenjem PPD-a i BOP-a te povećanjem CAL-a (32, 34). Djelotvoran je kad je riječ o nekoliko sistemskih i oralnih infekcija ili o regeneraciji mekog tkiva (24, 37). Zato se može očekivati da bi dodatna terapija AZM-om dala bolje rezultate. U našem istraživanju statistički su značajno smanjeni duboki džepovi i statistički su značajno povećani pričvrstci u svim točkama u skupini AZM+. Rezultati za GI bili su niži u skupini AZM+ u usporedbi sa skupinom AZM- tijekom cijelog istraživanja i ta je razlika također bila statistički značajna. Smatra se da je taj pozitivan ishod rezultat smanjenja parodontopatogena (38).

Terapija parodontitisa kod pušača izazov je jer njihov odgovor na liječenje ne mora zadovoljavati kao odgovor na liječenje kod nepušača. Broj popušenih cigareta na dan također može biti važan u liječenju parodontitisa. Dodatna antimikrobna primjena, uz mehaničko čišćenje, predložena je za intenziviranje ishoda terapije. Poboljšani klinički parametri uočeni su u istraživanjima s primjenom AZM-a kod teških pušača s kroničnim parodontitisom (7). Budući da se naša ispitivana populacija sastojala isključivo od pušača, procijenjen je učinak AZM-a u kombinaciji sa SRP-om. Smanjenje ukupnog broja dubokih džepova bilo je statistički značajno od početka tretmana do prvoga, trećeg i šestog mjeseca u objema skupinama. Broj plitkih džepova se povećao, što upućuje na to da su srednji i/ili duboki džepovi postali plići i pretvarali se u srednje/plitke džepove tijekom obaju protokola liječenja.

Međutim, smanjenje dubine džepova bilo je veće u skupini AZM+ nego u skupini AZM-. Smanjenje dubine džepova od prvoga do trećeg mjeseca i od prvoga do šestog mjeseca bilo je statistički značajno u skupini AZM+, a u skupini

tion in pocket depth from 1st to 3rd and from 1st to 6th months was statistically significant in AZM+ group, whereas the statistically significant reduction was only observed from 1st to 6th months in AZM- group. Changes in pocket depths from baseline to the first, third, and sixth months were greater in the AZM+ group for shallow, moderate, and deep pockets, and this difference was statistically significant. At all intervals, the reduction in pocket depths in the AZM+ group was statistically significantly greater than that in the AZM- group. These findings were consistent with trials indicating supplementary clinical advantages of local and/or systemic antimicrobials in adjunct to SRP (18-20).

When the entire study population was considered, the changes in the number of shallow pockets from baseline to first, third, and sixth months were statistically significant ($p<0.01$), with the increase in the number of shallow pockets being greater in the AZM+ group. Antibiotic administration significantly increased the pocket depth closure, in other words, the number of shallow pockets, at all time points. In the long run, the number of shallow pockets increased in the AZM+ group. Although the number of medium pockets decreased more significantly in the AZM+ group, the difference in change between baseline and other time points was not statistically significant in neither group ($p<0.05$). The decrease in pocket depths for medium pockets was similar at the first and third months, but it was significant at 6 months from baseline in the AZM+ group. The shift in the number of deep pockets from baseline to first, third, and sixth months was statistically significant ($p<0.01$), with the reduction in the number of deep pockets being greater in the AZM+ group as stated for shallow pockets.

The changes in CAL from baseline to first, third, and sixth months were statistically significant ($p<0.01$). The decrease was greater in the AZM+ group. The use of AZM resulted in a statistically significant decline on in pocket depths and an inclination in attachment gain. As a result, the use of azithromycin as an adjunct to SRP may be suggested, particularly in patients with shallow pockets where better results were indicated.

Changes in PI levels were alike in both groups. The reduction in PI from baseline to the first, third, and sixth months was statistically significant ($p<0.05$). When compared to the first month, the decrease in PI at the 3rd and 6th months was not statistically significant ($p<0.05$). The increase in PI observed at the sixth month was statistically significant compared with the third month ($p<0.05$) (Table 2). This increase in PI towards the end of the study could be attributed to patients' poor compliance.

Conclusion

The use of AZM as a supplement to non-surgical periodontal therapy has been shown to have a positive effect. The findings of our study, in which probing pocket depths were classified as shallow, medium, and deep in smoker periodontitis patients receiving adjunctive AZM therapy, confirmed the expected data. There are not many papers in the literature about the therapy outcomes of smoker periodontitis patients.

AZM- uočeno samo od prvoga do šestog mjeseca. Promjene u dubini džepova od početne vrijednosti do prvoga, trećeg i šestog mjeseca bile su veće u skupini AZM+ za plitke, umjerene i duboke džepove, a ta je razlika bila statistički značajna. U svim je intervalima smanjenje dubine džepova u skupini AZM+ bilo statistički značajno veće nego u skupini AZM-. Ti su nalazi bili u skladu s istraživanjima koja su upućivala na dodatne kliničke prednosti lokalnih i/ili sistemskih antimikrobnih lijekova kao dodatak SRP-u (18 – 20).

Kada se uzela u obzir cijela populacija u istraživanju, promjene u broju plitkih džepova od početne vrijednosti do prvoga, trećeg i šestog mjeseca bile su statistički značajne ($p < 0,01$), pri čemu je povećanje bilo veće u skupini AZM+. Primjena antibiotika značajno je povećala zatvaranje dubine džepova, drugim riječima, povećao se broj plitkih džepova u svim vremenskim točkama. Dugoročno je broj plitkih džepova porastao u skupini AZM+. Iako se broj džepova srednje dubine značajnije smanjio u skupini AZM+, razlika u promjeni između početne vrijednosti i drugih vremenskih točaka nije bila statistički značajna ni u jednoj skupini ($p < 0,05$). Smanjenje dubine džepova za srednje džepove bilo je slično u prvom i trećem mjesecu, ali je bilo značajno nakon šest mjeseci od početne vrijednosti u skupini AZM+. Pomak u broju dubokih džepova od početne vrijednosti do prvoga, trećeg i šestog mjeseca bio je statistički značajan ($p < 0,01$), pri čemu je njihovo smanjenje bilo veće u skupini AZM+ kao što je navedeno za plitke džepove.

Promjene u CAL-u od početne vrijednosti do prvoga, trećeg i šestog mjeseca bile su statistički značajne ($p < 0,01$). Smanjenje je bilo veće u skupini AZM+. Korištenje AZM-a rezultiralo je statistički značajnim smanjenjem dubine džepova i povećanjem pričvrstka. Kao rezultat toga može se predložiti uporaba azitromicina kao dodatka SRP-u, osobito za pacijente s plitkim džepovima kod kojih su postignuti bolji rezultati.

Promjene u PI razinama bile su podjednake u objema skupinama. Smanjenje PI-a od početne vrijednosti do prvoga, trećeg i šestog mjeseca bilo je statistički značajno ($p < 0,05$). U usporedbi s prvim mjesecom, pad PI-a u trećem. i šestom mjesecu nije bio statistički značajan ($p < 0,05$). Porast PI-a uočen u šestom mjesecu bio je statistički značajan u usporedbi s trećim mjesecom ($p < 0,05$) (tablica 2.). To povećanje potkraj istraživanja moglo bi se pripisati slaboj suradnji pacijenata.

Zaključak

Primjena AZM-a kao dopune nekirurškoj parodontološkoj terapiji pokazala se pozitivnom. Rezultati našeg istraživanja, u kojemu su dubine džepova klasificirane kao plitke, srednje i duboke kod pacijenata pušača s parodontitisom koji primaju dodatnu terapiju AZM-om, potvrdili su očekivane podatke. U literaturi nema mnogo radova o ishodima terapije parodontitisa kod pušača. Ispitivana populacija u ovom istra-

The study population of this study consisted of a small group of patients. Therefore, larger scale controlled clinical trials are required to identify the efficacy.

Conflict of Interest

Authors declare no funding and no conflict of interest.

Author's contribution: Concept – **E.Ü., N.B.**; Design – **E.Ü., N.B.**; Supervision – **E.Ü., N.B., M.C.**; Data Collection and/or Processing – **N.B., M.C.**; Literature Review - **E.Ü., N.B., M.C.**; Writing - **E.Ü., N.B., M.C.**; Critical Review – **E.Ü.**

živanju sastojala se od male skupine pacijenata. Zato su potrebna veća kontrolirana klinička istraživanja kako bi se utvrdila učinkovitost.

Sukob interesa

Autori navode da nisu bili u sukobu interesa.

Doprinos autora: **E. Ü., N. B.** – koncept i dizajn; **E. Ü., N. B., M. C.** – nadzor; **N. B., M. C.** – prikupljanje i/ili obrada podataka; **E.Ü., N. B., M. C.** – pregledavanje literature; **E. Ü., N. B., M. C.** – pisanje teksta; **E. Ü.** – kritički pregled

Sažetak

Svrha rada: Pušači s parodontitisom terapijski su izazovni. Azitromicin (AZM) se može upotrijebiti kao dodatak parodontološkoj terapiji. Svrha ovoga randomiziranoga, dvostruko slijepoga, kontroliranog kliničkog istraživanja bila je ustanoviti kod pušača učinak azitromicina na plitke, umjerene i duboke džepove u kombinaciji s nekirurškim parodontološkim liječenjem. **Materijal i metode:** U istraživanje je bilo uključeno 49 pacijenata koji su pušili najmanje 20 cigareta na dan dulje od pet godina, no samo je njih 40 obavilo sva mjerenja. Broj zuba, indeks plaka (PI), gingivni indeks (GI), dubina džepova (PPD), razina pričvrstka (CAL), krvarenje pri sondiranju (BOP) i recesija gingive zabilježeni su na početku liječenja te u prvom, trećem i šestom mjesecu. Dubine džepova grupirane su (PD) kao plitki, umjereni i duboki džepovi. U skupinu AZM+ (testna skupina) raspoređena su 24 pacijenta i oni su primali azitromicin (AZM; tablete od 500 mg) jedanput na dan tijekom tri dana, počevši od prvoga dana primjene parodontološkog liječenja. **Rezultati:** Pad ukupnog broja džepova u svim skupinama bio je statistički značajan od početne vrijednosti do prvog mjeseca, od početne vrijednosti do trećeg mjeseca i od početne vrijednosti do šestog mjeseca, te od prvog do trećeg mjeseca i od prvog do šestog mjeseca. Pritom se u objema skupinama statistički značajno povećao broj plitkih džepova između početne vrijednosti i trećeg mjeseca, početne vrijednosti i šestog mjeseca te prvog i šestog mjeseca (p = 0,000). **Zaključak:** Primjenom antibiotika znatno je povećan broj plitkih džepova u svim vremenskim točkama. Međutim, potrebna su opsežnija kontrolirana klinička istraživanja da bi se potvrdila učinkovitost AZM-a kod pušača s parodontitisom.

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Adresa za dopisivanje
dr. Melike CAMGOZ
Gazi Universitesi Dis Hekimligi Fakultesi
Ogretim Uyeleri (VIP) Klinigi
Emek Mah, Bişkek Cd. 1. Sokak
D:No:4
06490 Çankaya
Ankara / TURKEY
tel: +90 312 2034210
mlkozcan@yahoo.com

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