

Azithromycin treatment of drug induced gingival hyperplasia in renal transplant patients

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Abstract

Objectives: We conducted this study to evaluate and compare the efficacy of azithromycin treatment as an adjunctive therapy to oral hygiene measures in reducing drug-induced gingival hyperplasia in renal transplant patients under cyclosporine and those under tacrolimus therapy.

Material & Methods: Patients diagnosed with early to moderate gingival overgrowth with stable allograft function were included in the study. These patients had been taking either cyclosporine or tacrolimus for more than 6 months. The patients were randomized equally into three groups. Two groups had received 500-mg azithromycin for 5-days given at baseline only. While the control group received placebo in addition to the oral hygiene program. The clinical periodontal parameters were assessed and included the plaque index, bleeding on probing index, the gingival overgrowth index, and the probing depth. They were evaluated at the baseline and at follow up time (1, 3, 6 months).

Results: Seventy five kidney transplant recipients (48 men, 27 women) were included in this study. At the baseline time all groups were similar in the clinical parameters with no statistically significant difference ($P > .05$). At follow up time intervals all groups showed improvement over baseline measurements however both groups who received azithromycin showed more favorable results manifested by reduction of gingival bleeding and the depth of gingival sulcus. However, this improvement was more in the cyclosporine group than the tacrolimus group and the difference was statistically significant ($P > .05$).

Conclusions: Azithromycin is an effective therapeutic tool in the management of drug-induced gingival overgrowth as it is conservative, well tolerated, and rapidly effective with minimal side effects; especially in renal transplant patients under cyclosporine therapy.

Key words: Gingival hyperplasia, Azithromycin, cyclosporine, tacrolimus.



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Introduction

The increase in the number and life expectancy of renal transplant patients (RTP) has an impact on oral and dental health services. Different oral and dental problems arise in these patients, as a direct consequence of drug-induced immunosuppression or pharmacokinetics. Attention is now driven on the side effects of immunosuppression and on the quality of life (1, 2).

Gingival overgrowth (GO) is a well-known complication commonly seen with cyclosporine (CsA) and Tacrolimus (Tac) which are potent immunosuppressants universally used to prevent rejection of organ transplant with selective action on T lymphocytes and remarkable improvement in the survival rates of transplanted organs especially in renal allograft patients.(3,4) The prevalence of GO ranges from 20% to 35% for CsA treated patients , and approximately 14% for Tac group (5).The concomitant use of calcium channel blockers can also increase the severity of this condition. Such a variation in individual susceptibility can be as a result of the great number of inter-patient variables such as level of plaque control (directly correlated); gender (males are three times more sensitive); age (inversely correlated); and drug's daily dose (directly correlated (5-7).

The exact mechanism of cyclosporine-induced gingival hyperplasia remains a mystery, multiple mechanisms have been postulated like: (a) increased fibroblast stimulation, (b) collagen proliferation, and (c) bacterial-induced gingival inflammation. (8, 9, 10).

GO treatment modalities includes removing bacterial plaque, maintaining adequate oral hygiene, and, in some cases, surgical excision (gingivectomy and gingivoplasty). Nevertheless, the condition frequently relapses. Therefore to improve quality of life for those patients new treatment modalities need to be used. (10, 11)

In 1995, the efficacy of the macrolide antibiotic azithromycin (AZI) in the resolution of CsA-induced gingival hyperplasia was casually observed in two renal transplant recipients treated for respiratory infection. Subsequent studies confirmed these findings. (1-6, 12-15).

Accordingly, we performed this clinical study to investigate the effects of AZI as an adjunctive therapy in non-operative treatments of drug-induced gingival hyperplasia in (RTP) under CsA and Tac therapy. Up to our knowledge no previous research investigated the effect of AZI on Tac induced gingival hyperplasia which prompted this study.

Material and methods

This study was conducted after approval of the ethics committee at the Urology and Nephrology Centre, Mansoura University, Egypt and the purpose of the study was completely explained to each patient before entering the study and informed consents were obtained. The research was carried out in accordance with the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects.

Patients

Seventy five kidney transplant recipients diagnosed to have early to moderate GO entered the study. Criteria to enter the study were: Stable renal function (no change in serum creatine in the last 3 months), cyclosporine- or Tac based immunosuppression nonsmokers both males and females, age of > 16 years at the time of the study and no known allergy to macrolide antibiotics.

Exclusion criteria of patients were the following: A follow up less than 6 month, introduction of calcium-channel blockers therapy during the study and impaired renal function due to rejection during the therapy.

The quality of oral hygiene was evaluated by a subjective score into poor, regular, and good hygiene. This evaluation was based on the amount of bacterial plaque present and whether there was calculus using plaque disclosing solution.

Initial therapy was performed on all patients and consisted of full mouth scaling and root planing, by hand and ultrasonic instrumentation, and oral hygiene instruction. The plaque score was assessed at each scaling and root planing session, and oral hygiene instructions were reinforced. The oral hygiene program pursued the following therapeutic model: educational and motivational speech on oral hygiene, oral hygiene guidelines, and professional dental prophylaxis for plaque and calculus removal and home oral hygiene for 30 days.

This study was a double-blind clinical trial; neither the participants nor the researchers know which participants belong to the control group, as opposed to the test group. Only after all data have been recorded and analyzed do the researchers know the key that identifies the subjects and which group they belonged to.

The patients were randomized equally into three groups. Two groups received 500-mg AZI for 5-days given at baseline in addition to the oral hygiene program. While the control group received placebo in addition to the oral hygiene program.

Patients were randomized to receive either 500-mg /day of AZI or placebo. Trial medication was dispensed in identical capsules, prepacked in identical waterproof plastic pouches of 5 capsules each, coded using the alphabet. Randomization table, allocation details, and trial medication were reserved with a no-interest party, and were not revealed to the researchers until the study was over.

The clinical periodontal parameters were assessed by the same periodontist to minimise variability and also who was unaware of the treatment modality to eliminate any bias and these included: plaque index, bleeding on probing index, Gingival overgrowth index, and Probing depth. These were evaluated at the baseline and at follow up time (1, 3, 6 months).

The degree of GO was classified in four categories on the basis of hyperplastic index (HI) by Pernu et al, (17): Score 0; no GO, score 1; mild GO covering only the gingival one third of the tooth crown or less, score 2; moderated GO extending up to the middle of the crown, score 3; severe GO covering more than one half of the crown.

Immunosuppressive drug dose and level, time after transplantation, age and gender of the patients were assessed. Patients are screened regularly for whole blood and serum trough concentrations of CsA or Tac. Creatinine serum readings were measured as a monitor of renal function and were available as part of patient's routine examination on the transplant clinics.

Statistical analysis

Data were analyzed using SPSS Statistics software, version 19.0.0 (SPSS Inc, Chicago, Ill). Variations in the periodontal parameters over time were assessed using repeated-measures analysis of variance. Intragroup comparisons at follow up time (1, 3, 6 months) with baseline assessments were conducted using the paired t-test. Intergroup comparisons of the level of change in the periodontal parameters compared to baseline were conducted at each examination using Student's t-test.

Results

Demographic Data

A total 570 patients were screened from the outpatient Renal Transplant Clinic of the Urology-Nephrology Centre, Mansoura University, Egypt. Those patients had received kidney transplants between February 1992 to July 2009.

Seventy five patients (48 men, 27 women) who received kidney transplants with stable allograft function were re-

cruited. Their mean age was (33.63 ± 13.42 years, range 17–55 years); and the mean time since transplant was (59.66 ± 45.81 months, range 9–216 months).

The study groups

Group I (CsA with GO): twenty five patients, exhibiting CsA-induced GO (8 females and 17 males) aged from 20 and 49 years, mean of 31.6 ± 7.9 years).

Group II (Tac with GO): twenty five patients receiving tacrolimus therapy and exhibiting GO (10 females and 15 males) aged from 18 to 50 years, mean of 29.7 ± 9.5 years).

Group III Control group (CsA or Tac with GO): twenty five renal transplant patients receiving either CsA or Tac therapy with GO (9 females and 16 males) aged from 17 to 55, mean of 34.6 ± 7.9 years).

At the baseline time the three groups were similar in the clinical parameters with no statistically significant difference ($P > .05$). At follow up time intervals both groups who received AZI showed improvement over baseline measurements in clinical periodontal parameters over the study period ($P < .05$) manifested by reduction of gingival bleeding and the depth of gingival sulci. However, this improvement was more in the (CsA) group than the (Tac) group and the difference was statistically significant ($P < .05$). (**Table 1**)

The reported side effects were comparable in the two groups with accepted range which include diarrhea, nausea, slight abdominal pain and did not necessitate the stopping of the treatment in any case. Besides that the pharmacological therapy reduced the amount of gum bleeding, 60% of the patients reported that the treatment improved their appetite greatly as they could chew their food more easily and they also reported much easier tooth brushing.

AZI has shown effectiveness in reducing the amount of gingival overgrowth in both groups; however, it had a more consistent impact in the CsA Group. When the baseline gingival measurements were compared with interval post-therapy measurements, there was sustained improvement in gingival overgrowth throughout the entire 6 months time period. As in CsA group 72% showed complete healing 16% no improvement and 12% relapse. In Tac group 48% showed complete healing 36% no improvement and 16% relapse. While in control group 28% showed complete healing 52% no improvement and 20% relapse. And the difference was statistically significant between the three groups ($P < .05$). (**Figures 1-4**)

Table 1. Intragroup comparisons of periodontal parameters at different time intervals

Variable	Baseline Mean (SD)	1 month Mean (SD)	3 month Mean (SD)	6 month Mean (SD)
CsA group				
PI (% of sites)	93.4 (5.7)	54.6 (9.7)*	50.6 (6.6)**	51.3 (4.6)**
BOP (% of sites)	50.5 (15.7)	15.3 (9.7)**	21.7 (10.5)*	20.7 (8.5)*
PPD (mm)	0.90 (1.0)	0.22 (0.7)**	0.20 (0.9)**	0.25 (0.4)**
GOI (% of sites)	35.7 (12.9)	5.9 (5.5)***	7.8 (3.8)***	8.3 (4.5)***
Tac group				
PI (% of sites)	90.3 (4.3)	66.4 (6.5)	64.8 (8.1)*	63.5 (7.5)*
BOP (% of sites)	56.2 (8.3)	25.4 (15.7)*	26.7 (11.4)**	28.7 (10.4)**
PPD (mm)	0.75 (0.9)	0.43 (0.7)	0.37 (0.5)**	0.35 (0.7)**
GOI (% of sites)	37.6 (13.7)	13.3 (10.5)	15.8 (7.5)*	18.8 (5.5)*
Control group				
PI (% of sites)	95.3 (4.3)	85.4 (6.5)	83.8 (8.1)*	80.6 (6.6)*
BOP (% of sites)	56.2 (8.3)	50.4 (15.7)*	48.7 (14.4)**	41.7 (12.5)**
PPD (mm)	0.85 (0.6)	0.53 (0.7)	0.31 (0.7)**	0.30 (0.9)**
GOI (% of sites)	37.6 (13.7)	33.3 (7.5)	30.8 (5.5)*	33.0 (5.8)*

* $P, .05$; ** $P, .01$; *** $P, .001$ (paired t-test statistics).



Figure 1. CsA patient with moderate gingival overgrowth at baseline.



Figure 2. Same patient after 6 months with complete gingival healing.



Figure 3. Tac patient with upper mild and lower moderate gingival overgrowth at baseline.



Figure 4. Same patient after 6 months with gingival improvement only in the upper jaw while no improvement in the lower jaw.

Discussion

Patient compliance with antibiotic regimens is generally a problem. However, due to the small number of tablets in the course and lack of significant side effects, it is likely that compliance is not an issue for people prescribed AZI in the present study.

While dentists usually view antibiotics in the context of their role in controlling infections, AZI has much broader properties which potentially account for the improvement in periodontal health. Hirsch et al. (2012) reported that a chronic periodontitis patient receiving AZI treatment without concomitant periodontal therapy had alveolar bone regeneration raising the intriguing possibility that azithromycin encourages bone formation once tissue inflammation has subsided. He stated that "it is more than an antibiotic" (14).

Pharmacological properties of AZI that makes it a desirable agent in the management of dental infections include: stable in acid pH, well absorbed, absorption not affected by food, sustained high tissue concentrations, extensive penetration of cells, rapid uptake by phagocytes, delivery in high concentrations to site of infection, once daily delivery, and short duration of treatment (12).

Following oral administration of AZI, high tissue concentrations are found, which are sustained long after serum concentrations have declined to very low levels. AZI extensively penetrates cells, including tissue fibroblasts. It is also rapidly and extensively taken up by phagocytic cells (polymorphonuclear leukocytes and macrophages). This produces intracellular concentrations far greater than those in the extracellular medium. (12-15).

It is hypothesized that AZI is delivered to a site of infection by two mechanisms: Firstly, by direct uptake into tissues, which in part is by fibroblasts. Secondly, phagocytes deliver the drug to sites of infection where it is released in response to phagocytosis producing effective, locally high concentrations of the drug by a biological targeted delivery mechanism. The preferential uptake by phagocytes leads to concentrations in infected tissues, which are much higher than in similar non infected sites (12-15).

GH improvement with the use of AZI might be related to the antibiotic effect of this drug, eliminating oral bacteria, reducing local inflammation, and decreasing the extracellular matrix by fibroblasts. In fact, some researchers observed a decrease in the growth of aerobes and spirochetes with the use of AZI (9-11). Kim et al. (8) have shown in their in vitro study that AZI blocked fibroblast proliferation and collagen synthesis (initiated by cyclosporine) and activated fibroblast MMP-2.

On the other hand, attempts to isolate pathogenic agents in gingival fragments with CsA-induced GH were not consistent. (18, 19) Moreover, the beneficial effect of azithromycin on GH was not clearly demonstrated with other antibiotics. Whereas Mesa et al. (22) and Aufrecht et al. (23) were not successful in controlling CsA-induced GH using metronidazole for seven days. Moreover, a study testing the efficacy of metronidazole and azithromycin in controlling CsA-induced GH has shown that the latter was significantly more effective (20). Further studies are needed to confirm the results achieved in this study and to clarify the reasons for the differences of response to Azithromycin among renal transplant patients.

Conclusion

Azithromycin is an effective therapeutic tool in the management of drug-induced gingival overgrowth as it is conservative, well tolerated, and rapidly effective with minimal side effects; especially in renal transplant patients under cyclosporine therapy. Prescription of antibiotics is not substitute for adequate debridement, good oral hygiene and regular maintenance care.

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