Review Article

The efficacy of azithromycin on cyclosporine-induced gingival enlargement: Systematic review and meta-analysis

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ABSTRACT

Background: Cyclosporine is one of the powerful immunosuppressant drugs commonly used to avoid transplant rejection and autoimmune condition management. However, this drug has many side effects, such as nephrotoxicity, hepatotoxicity, hypertension, and gingival overgrowth. Gingival enlargement is one of the most commonly reported adverse drug outcome in patients with long term usage of the drug with the exclusion of other confounding factors. Hence, this systematic review and Meta-analysis was planned to investigate the effect of azithromycin on cyclosporine A-induced gingival enlargement.

Methods: We used 4 electronic databases: MEDLINE (up to January 2018), EMBASE (up to January 2018), CINAHL (up to January 2018), Cochrane Library (up to January 2018) to search all the available literature between February 1, 2018, and January 1, 2019. All papers, published up to January 2018, on the efficacy of azithromycin on cyclosporine-induced gingival enlargement were included on this systematic review and meta-analysis. RevMan 5.3 software was used to make the quantitative analysis and the pooled effect presented in terms of the mean difference. Meanwhile, the presence of heterogeneity is presented in terms of I^2 .

Results: Five Randomized controlled trials with a total of 167 participants were eligible for this study. The effect of azithromycin on cyclosporine-induced gingival growth, probing depth and plaque index was reported in 3 studies and the selected 5 studies reported its effect on bleeding on probing. The pooled effect revealed there was a significant reduction of gingival enlargement (MD, 1.58, 95%CI: 0.77–2.39) and bleeding on probing in the intervention group (MD, 1.32, 95%CI: 0.39–2.24). Statistically non-significant effects were observed on the effect of azithromycin on plaque index and probing depth in patients with cyclosporine-induced gingival enlargement.

Conclusion: Azithromycin has a clinically significant effect on the reduction of cyclosporine-induced gingival enlargement and bleeding on probing.

1. Introduction

Drug-induced gingival overgrowth or enlargement occurs in whole or in part from systemic drug use. It occurs as a side effect following the administration of drugs used for treatment of various medical illnesses. And thus, the overgrowth cannot be explained as a variation of the intended pharmacological action of the drug.¹

It was a must to prescribe the most powerful immunosuppressant after organ transplant is done to prevent graft-host reaction and cyclosporine is one of those drugs.^{2,3} Even if, its immunosuppressive effect has a beneficial effect for the patient, the presence of several adverse effects such as; hepatotoxicity, nephrotoxicity, gingival enlargement, and hypertensive make the treatment difficult to the patients and physicians.^{4,5}

The enlargement of the gingiva has a significant effect on the aesthetic, function, speech and oral hygiene maintenance of the patients. Several studies revealed the presence of some temporary improvement of the gingival enlargement and periodontal condition with surgical and non-surgical periodontal therapy.^{6–9} The enlarged gingiva (pseudo pocket) due to the drug facilitates the retention of bacterial plaque and predispose the person to dental caries, and periodontal disease.^{10,11}

Azithromycin has been reported as manner an inhibitory effect on CsA-induced GO in human.¹² A study done in Spain revealed that AZM has a positive effect on gingival growth in patients receiving cyclosporine and Nifedipine combination treatment.¹³ Although azithromycin is effective in the management of periodontal infections (both as topically on sub gingival approach¹⁴ and systemic administration¹⁵) its effect on cyclosporine induced gingival enlargement is controversial.

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Fig. 1. Flow diagram showing the article selection process.

To date, there has been no clear-cut literature which could consolidate the management of cyclosporine-induced gingival growth. There is a need of exposition which would refine our knowledge about the antibiotic treatment of this side effect. The aim of this literature review is to bring a focus on integrated knowledge about cyclosporine-induced gingival overgrowth and the effect of azithromycin on it.

2. Methods

This systematic review and meta-analysis were done using PRISMA (Preferred reporting items for systematic review and Meta-analysis) checklist.¹⁶

Eligibility criteria.

- Randomized Controlled Trials (RCTs)
- Patients with a clinical diagnosis of Cyclosporine -induced gingival enlargement
- The intervention groups took azithromycin with or without scaling and root planning while the control groups received placebo or other antibiotics

2.1. Outcomes of the study

The primary outcomes of the selected studies were mean gingival overgrowth index (GOI), pocket probing Depth (PD), bleeding on probing (BOP), and plaque index (PI).

2.2. Information sources

We used 4 electronic databases: MEDLINE (up to January 2018), EMBASE (up to January 2018), CINAHL (up to January 2018), Cochrane Library (up to January 2018) and scanning reference lists of

articles using manual search to explore relevant studies on the effect of azithromycin in cyclosporine-induced gingival enlargements. All articles were searched irrespective of language. The search was started on February 1, 2018, and ended on January 1, 2019.

2.3. Data search strategy

To search all the relevant clinical trials we used the following search keywords in the above-listed databases; gingival enlargement, gingival overgrowth, cyclosporine, azithromycin, gingival overgrowth, bleeding on probing. Using the above keywords article search was done using Boolean operations (gingival enlargement OR GE OR gingival overgrowth) and (cyclosporine OR CsA) AND (azithromycin OR AZM).

2.4. Article selection

Three authors (AT, BG and ZA) searched the articles electronically using the databases and manually using Google scholar. The identified papers were exported to Endnote and duplicated papers were identified and removed by one reviewer (AT).

The articles retrieved were evaluated for the availability of all the necessary data and its eligibility by two reviewers independently (BG and ZA). The conflict between the two reviewers was settled by the involvement of the third (AT) reviewer. After the removal of the duplicated and non-eligible papers, the remaining articles were screened based on their abstracts and titles. Full texts of the screened articles were deeply assessed and papers which didn't meet the eligibility criteria were excluded from this systematic review and meta-analysis (Fig. 1).

Table 1

The characteristics of the study participants with their outcomes.

Authors name/country,year	Mean age	Study design	Sample size	Participants medical condition	Type of drug taken
Argani et al. ¹⁹ , Iran, 2006	36.80 ± 12.89	RCT	20	Renal transplanted	Cyclosporine
Aboelsaad et al., Egypt, 2013	33.63 ± 13.42	RCT	75	Renal transplanted	
Ramvalho et al., ²⁰ Brazil, 2007	29.6 ± 4.7. I 34.5 ± 3.0. C	RCT	20	Renal transplanted	
Chand et al., USA, 2004	17.18 ± 7.82 I 17.71 ± 4.55C	RCT	25	Renal transplanted	
Mesa et al., ²¹ Spain, 2003	41.9 ± 14: I 43.3 ± 10: C	RCT	27	Renal transplanted	

Parameters measured	Type of intervention	Results	Outcomes
1. ● Gingival overgrowth index ● Bleeding on propping ● Plaque index ● Probing depth	I:AZM containing toothpaste (85 mg azithromycin per gram of tooth paste for 1 month) C: placebo toothpaste,	GOI, I: 1.1 ± 0.56 to 0.51 ± 0.47, <i>P</i> = .005); C: 0.57 ± 0.51 to 0.52 ± 0.44, <i>P</i> = .22). Plaque index: I: 54.1 ± 15.3–17.9 ± 6.2, C: 44.3 ± 16.9–15.3 ± 4 BOP I: 0.44 ± 0.14–0.1 ± 0.08, C:0.35 ± 0.18–0.18 ± 0.14 Probing depth: Intervention: 8.9 ± 1.9–7.4 ± 1.2 Control: 7.9 ± 1.3—7.35 ± 1.3	Azithromycin-containing toothpaste is an effective, simple, and noninvasive treatment for CyA-induced gingival overgrowth.
2. ● plaque index, ● bleeding on probing index ● Gingival overgrowth index ● Probing depth	I: 500-mg AZI for 5-days + OHI C: placebo	Intervention: cyclosporine: PI: I, 93.4 (5.7) –51.3 (4.6) at the end of 6th month C: 95.3 (4.3)–80.6 (6.6) BOP: intervention: 50.5 (15.7) –20.7 (8.5) Control: 56.2 (8.3) –41.7 (12.5) GOI: intervention: 35.7 (12.9) –8.3 (4.5) Control: 37.6 (13.7) –33.0 (5.8) Probing depth: Intervention: 0.90 (1.0) to 0.25 (0.4) Control: 0.85 (0.6) to 0.30 (0.9) ● Intervention: PI: 1.52 (0.28) to 0.50 (0.16) (<i>p</i> < 0.01) 15days, and 0.46(0.14) on day 30 (<i>p</i> < 0.01), 60 day: 0.33 ± 0.15 Calculus index (CI): base: 0.62 ± 0.14 15 day:0.28 ± 0.12 30days: 0.33 ± 0.12 60 day: 0.26 ± 0.19 oral hygiene index ● 2.20 ± 0.36, base ● 0.73 ± 0.25, 15 days ● 0.80 ± 0.24, 30days ● 0.59 ± 0.17.60 days GOI ● 1.90 ± 0.27, baseline ● 0.90 ± 0.27, 15days ● 0.70 ± .21, 30days ● 0.40 ± .24, 60 days Control group PI: 1.50 ± 0.34 *1.02 ± 0.28*1.54 ± 0.29*0.90 ± 0.33, CI: 0.65 ± 0.14*0.42 ± 0.15*0.35 ± 0.13*0.36 ± 0.22 OHI: 2.15 ± 0.33*1.44 ± 0.28*1.80 ± 0.31*1.13 ± 0.38. GOI: 1.50 ± 0.22*1.40 ± 0.22*1.40 ± 0.22*1.20 ± 0.20	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.
3. ● Plaque index ● Calculus index ● Oral hygiene index ● Gingival overgrowth index	I: OHP+ Azithromycin 500 mg for 3days C: OHP	● Intervention: PI: 1.52 (0.28) to 0.50 (0.16) (<i>p</i> < 0.01) 15days, and 0.46(0.14) on day 30 (<i>p</i> < 0.01), 60 day: 0.33 ± 0.15 Calculus index (CI): base: 0.62 ± 0.14 15 day:0.28 ± 0.12 30days: 0.33 ± 0.12 60 day: 0.26 ± 0.19 oral hygiene index ● 2.20 ± 0.36, base ● 0.73 ± 0.25, 15 days ● 0.80 ± 0.24, 30days ● 0.59 ± 0.17.60 days GOI ● 1.90 ± 0.27, baseline ● 0.90 ± 0.27, 15days ● 0.70 ± .21, 30days ● 0.40 ± .24, 60 days Control group PI: 1.50 ± 0.34 *1.02 ± 0.28*1.54 ± 0.29*0.90 ± 0.33, CI: 0.65 ± 0.14*0.42 ± 0.15*0.35 ± 0.13*0.36 ± 0.22 OHI: 2.15 ± 0.33*1.44 ± 0.28*1.80 ± 0.31*1.13 ± 0.38. GOI: 1.50 ± 0.22*1.40 ± 0.22*1.40 ± 0.22*1.20 ± 0.20	Azithromycin associated to efficient OHP induced a striking reduction in cyclosporine-induced gingival over growth
4. Gingival growth index	Intervention: azithromycin 500 mg for 5days Control: Metronidazole 500 mg for 7days	Intervention: ● Gingival over growth > Baseline: 12.87 ± 0.40 > 2 week: 11.27 ± 0.33 > 1 month: 12.20 ± 0.36 > 3month: 11.44 ± 0.28 > 6month: 11.41 ± 0.34 Control group ◆ Baseline: 13.13 ± 0.29 ◆ 2 week:12.71 ± 0.26 ◆ 1 month:12.93 ± 0.30 ◆ 3month: 12.49 ± 0.26 6month: 11.13 ± 0.24	Azithromycin to be more effective than metronidazole. Therapy with azithromycin offers an effective alternative to the management of CyA-induced gingival overgrowth
5. Gingival over growth index	I: AZM 500 mg for 7days C: placebo	Intervention: Baseline: 0.932 ± 0.11 1month: 0.909 ± 0.15 Control: Baseline: 1.073 ± 0.32 1month: 0.962 ± 0.22	A 7-day course of AZM does not induce remission of CsA induced GO, although it acts on concomitant bacterial over-infection and gingival inflammation.

AZM: Azithromycin, C: Control, CI: Calculus index, PD: Probing depth, OHP: or al hygiene program, BOP: Bleeding on probing, PI: Plaque index, CyA: Cyclosporine A, I: intervention, GOI: Gingival overgrowth index, OHI: Oral hygiene index.

2.5. Data extraction and quality assessment

From the selected RCTs, all relevant data was extracted by the three

investigators (AT, BG and ZA). The following variables were extracted for the selected articles; author name, country of study, publication year, study design, periodontal condition of the patient, type of

Fig. 2. Risk of bias assessment of the included studies.

intervention and control, the outcome of the study (Table 1).

Quality of the study was assessed using the Cochrane tools for risk of bias assessments.¹³ The assessment checklist has the following parameter; random sequence generation, allocation concealment, the blindness of the participants and personnel, blinding of the outcomes, incomplete outcome data, selective exposure, and other biases.

2.6. Statistical analysis

The primary outcome of the study was gingival enlargement, bleeding on probing, plaque index and. The meta-analysis was done using RevMan 5.3 software.¹⁷ The pooled effect of azithromycin on gingival enlargement due to cyclosporine in presented using random-effect Model and the heterogeneity was quantified using the I^2 .

3. Results

3.1. Search yield

Twenty-six papers were initially identified using the selected electronic databases. Of the searched articles 6 were duplicates. After a

detailed screening of the titles, abstracts and references 9 articles were removed. The remaining 11 articles were screened using the full text and 6 articles were excluded since they didn't meet the inclusion criteria. The included 5 studies included in both qualitative and quantitative synthesis (See Fig. 1).

3.2. Characteristics of the included studies

One hundred sixty-seven participants were included in the selected five articles to show the effectiveness of azithromycin on cyclosporine induced gingival enlargement. Among the included trials; one was from Iran, one from Egypt, one from USA and one study was done in Spain. All trials were done since January 2018 and the search was done irrespective of language deference.

Majority of the trials had initial oral hygiene therapy on all patients using full-mouth scaling and root planning and all the included participants had a stable renal function (serum creatinine < 2 mg/dl) (Table 1).

3.3. Intervention

All the intervention group received azithromycin 500 mg while the control group received either placebo or other antibiotics (Table 1).

3.4. Outcome

The primary outcome assessed in the included studies was gingival growth index (GOI), plaque index (PI), bleeding on probing (BOP) and Probing depth (PD) (see Table 1).

3.5. Risk of bias assessment

The risk of bias in the included studies was assessed using Cochrane collaboration's tool for risk of bias assessment for RCTs.¹⁸ Majority of the included studies has random sequence generation and concealed allocation (Fig. 2).

3.6. Qualitative analysis of the effect of azithromycin on cyclosporine-induced gingival enlargement

A RCTs done in Iran in 2006, on the effect of azithromycin on cyclosporine-induced gingival enlargement revealed that azithromycin containing toothpaste is an effective, simple and non-invasive treatment for cyclosporine-induced gingival enlargement.¹⁹

A RCTs done in Egypt in 2013 showed that azithromycin is an effective therapeutic tool for gingival enlargement, bleeding on probing, and probing depth.²⁰

Another study done in Spain showed that a 7-day course of azithromycin doesn't induce gingival remission of cyclosporine-induced gingival enlargement. However, there is a positive effect on the prevention of bacterial over infection and gingival inflammation.²¹

The effect of azithromycin on cyclosporine-induced gingival growth/enlargement is summarized in Table 1.

Fig. 3. The pooled effect of azithromycin on gingival growth index on cyclosporine induced gingival enlargement.

Fig. 4. The pooled effect of azithromycin on bleeding on probing (BOP) on cyclosporine induced gingival enlargement.

Fig. 5. The pooled effect of azithromycin on plaque index on cyclosporine induced gingival enlargement.

Fig. 6. The pooled effect of azithromycin on probing depth on cyclosporine induced gingival enlargement.

3.7. Quantitative analysis of the effect of azithromycin on cyclosporine A-induced gingival enlargement

3.7.1. Azithromycin on gingival growth index

One hundred fifteen participants with renal transplant were participated in the clinical trial to show the effect of azithromycin. The pooled meta-analysis revealed that there was a reduction of gingival growth with a mean difference of 1.58 (95%CI: 0.77–2.39). This reduction is significant ($p = 0.0001$) (Fig. 3).

3.7.2. The effect of azithromycin on bleeding on probing

One hundred seventy-six patients were involved in the study (99 in the control and 77 in the intervention). Azithromycin significantly decreasing the incidence of bleeding on probing in patients with gingival enlargement with a mean difference of 1.32 (95%CI: 0.39–2.24, $p = 0.005$) (Fig. 4).

3.7.3. The effect of azithromycin on the plaque index

The meta-analysis revealed that azithromycin has a reduction effect on the plaque index but it is non-significant (11.83; 95%: -9.76, 33.42) with a p -value of 0.28 (Fig. 5).

3.7.4. The effect of azithromycin on probing depth

Azithromycin has no significant effect on the reduction of probing depth in patients with gingival enlargement due to cyclosporine A ($p = 0.08$) (Fig. 6).

4. Discussion

The enlargement of the gingiva has a significant effect on the aesthetic, function, speech and oral hygiene maintenance of the patients.

This meta-analysis, comprises of 5 RCTs, tries to assess the effect of azithromycin on cyclosporine-induced gingival enlargement. The intervention groups received azithromycin while the control groups took placebo or other antibiotics.

A systematic review done in 2008 on the efficacy of AZM on cyclosporine A-induced gingival enlargement revealed that a 5-day course of Azithromycin with Scaling and Root Planning reduces the degree of gingival overgrowth.²² The present study revealed a similar result that azithromycin has a significant effect on the reduction of gingival enlargement on patients with cyclosporine A-induced gingival enlargement. It showed the pooled effect in terms of mean difference of 1.58(95%CI: 0.77–2.39). The previous study didn't show the pooled effect of azithromycin on cyclosporine-induced gingival enlargement due to limited studies.²² Meanwhile, Azithromycin has a statistically significant effect of reducing bleeding on probing tendencies in patients with cyclosporine-induced gingival enlargement with a mean difference of 1.32(95% CI: 0.39–2.24).

This quantitative analysis also revealed that azithromycin has no significant effect on plaque index (11.83, 95%CI: -9.76, 33.42) and probing depth (0.29, 95%CI: -0.03, 0.61). This is due to the fact that plaque index and probing depth showed the presence of true periodontal disease in patients while gingival enlargements are a pseudo enlargement due to the drug that have no alveolar bone loss.

During this systematic review and meta-analysis, we faced a shortage of studies and two of the included studies didn't indicate the status of the gingival growth index. Also there is no previous similar meta-analysis to discuss on the impact of azithromycin on probing depth and bleeding on probing and other periodontal parameters.

5. Conclusion

This study provides that azithromycin is clinically effective in reduction of gingival enlargement index and bleeding on probing in patients with cyclosporine A-induced gingival enlargement.

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Authors' contribution

AT: Conception of the study, designing the study, article search, data analysis, quality assessment, manuscript writing.

BG: Designing the study, article search, quality assessment, manuscript writing.

ZA: Designing the study, article search, quality assessment, manuscript writing.

Ethics approval and consent to participate

Not-applicable.

Consent for publication

Not-applicable.

Availability of data and materials

All the supporting documents of these articles are available in <https://github.com/Ameix/AZM/tree/Ameix-patch-1>.

Declaration of competing interest

The authors declare there is no competing interest.

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Abbreviations

AZM	Azithromycin
BOP	Bleeding on probing
PI	Plaque index
GOI	Gingival overgrowth index
GE	Gingival enlargement

RCTs	Randomized controlled trial studies
CI	Confidence interval

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