Does systemically administered azithromycin have an effect on gingival overgrowth? A systematic review

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Objective. The aim of this systematic review was to evaluate studies that analyzed the effect of systemically administered azithromycin (AZM) on cyclosporine A (CsA)-mediated gingival overgrowth (GO).

Study Design. A systematic literature search was performed for publications published by January 1, 2019, using electronic databases and hand search. Human clinical trials (>10 patients) with systemic administration of AZM and a follow-up of ≥6 months, published in the English or German language, were included.

Results. From 266 titles identified, 6 publications with data from 104 patients were included. A great heterogeneity in terms of sample size, administration/dosage regimen of AZM, consideration of potential confounders and measurement of GO was observed. Treatment duration with AZM ranged from 3 to 5 days with a maximum dosage of 500 mg/day, gingival response was measured by using various scoring systems. A synthesis of results, by using a vote counting method, was applied. In all included studies, a beneficial effect of systemically administered AZM with respect to a reduction of GO was documented.

Conclusions. Limited evidence from 6 case series suggests a positive effect of systemically administered AZM on the reduction of CsA-mediated GO. Azithromycin may be considered a potential alternative to surgical reduction of GO. (Oral Surg Oral Med Oral Pathol Oral Radiol 2019;128:606−614)

Gingival overgrowth (GO), according to the new classification of periodontal and peri-implant diseases and conditions: Drug-induced gingival enlargement,[1] is a common side effect of certain medications, including cyclosporine A (CsA). This oral complication affects 21% to 35 % of renal transplant recipients and may lead to aesthetic constraints, pain, periodontal inflammation, and subsequent bone loss.[2-5]

Several therapeutic approaches, including plaque control, scaling and root planning, and periodontal surgery, including gingivectomy, have been described.[6,7] However, an interesting observation was first described in a case report of a patient with a pulmonary infectious disease. A marked reduction of GO occurred after antibiotic treatment with systemically administered azithromycin (AZM), without any further periodontal therapy.[4] The effect was explained as a side effect of AZM. Biochemically, it was shown that AZM may improve the symptoms of CsA-induced GO, by blocking CsA-induced cell proliferation and collagen accumulation and by activating matrix metalloproteinase-2 in gingival fibroblasts.[8]

The aim of this systematic review was to evaluate studies that analyzed the effect of systemically administered AZM on GO.

MATERIALS AND METHODS

Protocols

The review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) criteria (Figure 1).[9,10] The research question was explored using the PI(E)CO (Population, Intervention/Exposure, Comparison, Outcomes) method.

The specific question addressed was "In patients suffering from drug-induced GO, does systemically administered AZM have a beneficial effect on remission of GO, after an observation period of ≥6 months?"

Search strategy

The electronic bibliographic databases MEDLINE/PubMed, EMBASE and Cochrane Library were searched for citations included as of January 1, 2019. Unpublished reports were identified by searching the OpenGrey (formerly OpenSIGLE) database that lists unpublished literature (http://www.opengrey.eu/). The search protocols within the different databases were applied and validated as identically as possible. Combinations of the validated search terms for MEDLINE/

Statement of Clinical Relevance

Limited evidence presented in this systematic review suggests that the systemically administered antibiotic azithromycin may reduce gingival overgrowth induced by cyclosporine A and may serve as an alternative first approach to surgical management.

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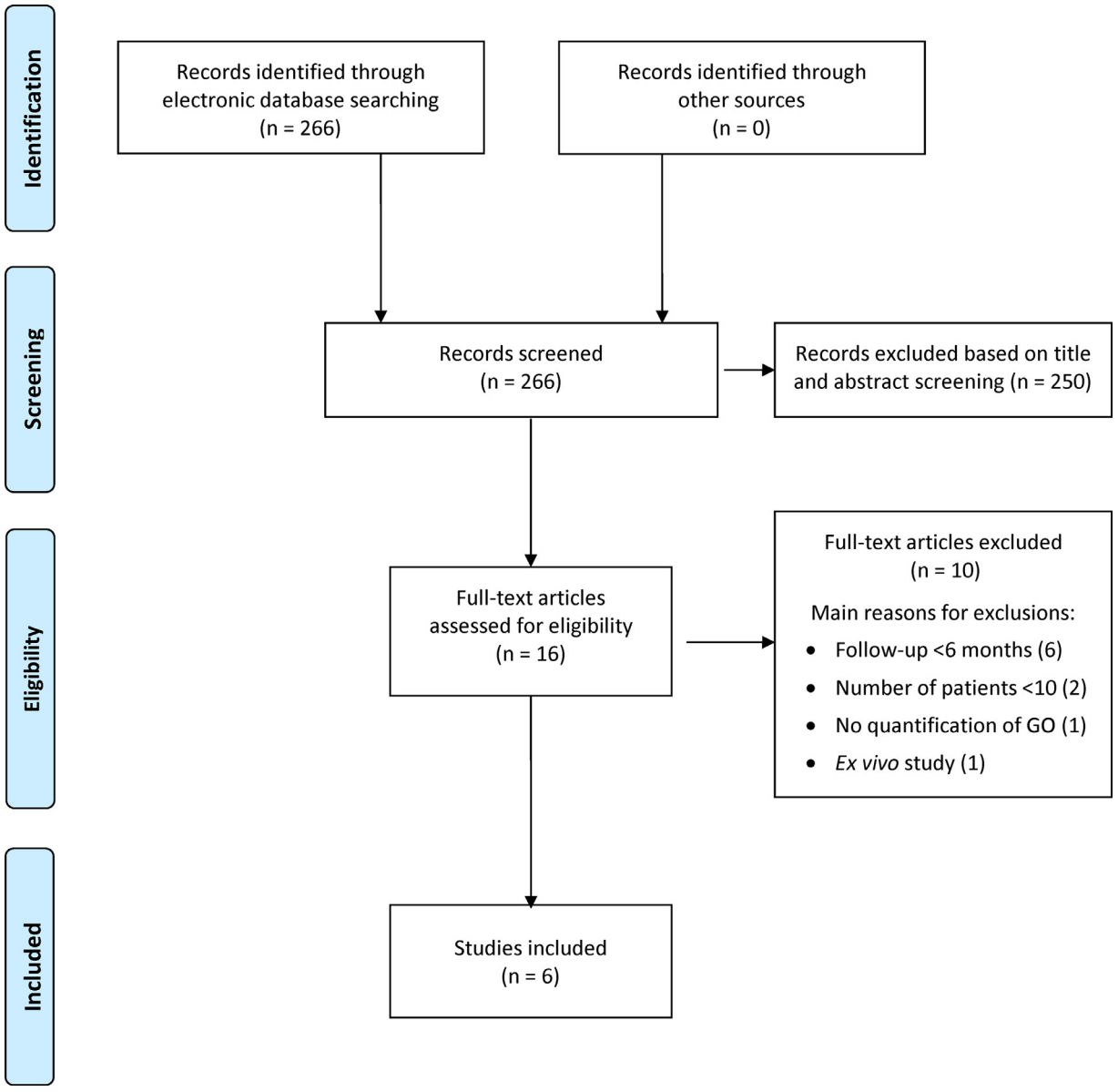

Fig. 1. Selection process for the studies included.[10]

PubMed, EMBASE, and Cochrane Library were "Gingival Overgrowth" AND "Azithromycin," "Gingival Hyperplasia," AND "Azithromycin," as well as "Periodontal Diseases" AND "Azithromycin" (see Appendix S1). Additionally, potentially relevant citations were harvested from the bibliographies of included studies and examined for inclusion eligibility. The references resulting from the searches were entered in EndNote (Version X9; Clarivate Analytics, Philadelphia, PA), and duplicates were removed.

Inclusion criteria

The search was limited to original research investigating the effects of systemically administered AZM on GO. Inclusion criteria were publication in the German or English language; human clinical trials (case series >10 patients, randomized controlled trials); presence of GO (i.e., interdental and/or marginal gingiva appears greater than would be expected from a gingival inflammation alone[1]; at least a single tooth affected per patient) and quantification of GO (gingival measurements in millimeters or application of a scoring system to grade severity of GO); systemic administration of AZM; follow-up of at least 6 months.

Exclusion criteria

Studies were excluded for the following reasons: no quantification of GO; local administration of AZM (no

systemic administration of AZM); surgical treatment without administration of AZM; in vitro or ex vivo studies, reviews or case reports (<10 patients); study not performed in humans/animal experiments.

Review process

Two of the authors (M.F., S.M.) screened the titles for potential eligibility, according to the inclusion criteria. Discrepancies in scores allocated to publications were discussed among the authors until a consensus was reached.

Outcome measures

The primary outcome measure was reduction of GO, determined by a reduction within the individual scoring system applied in the study[11-14] or by reduced gingival measurements in millimeters.[2,15]

Data extraction

The following data were collected in data extraction files (Microsoft Excel, Version 16.16.8; Microsoft Corp., Redmond, WA): Sample size, demographic data, follow-up time, oral hygiene, gingival surgery, dosage and administration regimen of AZM, medication (potentially) causing GO, interruption of GO causing medication during the study, adverse events, criteria of GO assessment, degree of GO at baseline and at follow-ups, and the result of the used vote counting method, that is, benefit of systemically administered AZM on the reduction of GO is present or not (Tables I and II).

Summary measure

Because of the pronounced heterogeneity with respect to treatment protocol and outcome measures, as well as variations in study populations, sample sizes, and/or statistical methods, a synthesis of the results of the included studies, by using a vote counting method, was applied (see Table II).[16] This means that the overall outcome of each study was summarized as positive—that is, a benefit of systemically administered AZM on the reduction of GO was present—or negative—that is, no such benefit existed. Subsequently, the number of positive studies was compared with the number of negative studies to answer the question if there is evidence for a beneficial effect of AZM intake in terms of reduction of GO.

Quality assessment

The methodologic and reporting quality of included case series was evaluated by the checklist from Moga et al.,[17] including 18 items of the following topics: (1) study objective; (2) study population; (3) intervention and co-intervention; (4) outcome measure; (5) statistical analysis; and (6) results and conclusion (see Appendix S2). With regard to the adequacy of the respective case series, the items were graded, and the percentage of positively graded items was calculated (Table III).

RESULTS

The selection process is shown in Figure 1. Out of 266 titles identified through electronic and hand searches, 16 studies were selected after abstract screening and assessed by performing full-text review. Finally, 6 studies were considered eligible for this analysis. The reasons for exclusion are shown in Figure 1 and in Appendix S3.

Summary of studies

The characteristics according to the PICO analysis (Population, Intervention, Comparison, Outcomes) are shown in Tables I and II.

Population

The characteristics of the population are shown in Table I. Clinical trials comprised 104 participants, with 39 women, treated with AZM. Studies included a minimum of 11[11] up to 31[12] patients (mean age range 17−48 years).[12,15] All patients in the studies included received CsA. Three studies evaluated oral hygiene levels at baseline.[2,12,14] By using a classification of good and poor, oral hygiene was assessed as poor in 12 of 31 patients, and 19 of 31 patients showed good oral hygiene levels.[12] In another study, a classification of good, moderate, and poor was applied.[2] Three of 12 patients showed moderate oral hygiene, and 9 of 12 patients demonstrated poor oral hygiene levels.[2] In 1 study, a significant correlation between oral hygiene and GO was observed (i.e., 8 of 12 patients with poor oral hygiene demonstrated the highest GO scores in contrast to 4 of 19 patients with good oral hygiene).[12]

At baseline, all patients presented with GO (see Table II). GO was defined by using different measures—that is, scores[11-14] based on a previously published scoring system,[3,18] or measurements in millimeters.[2,15] No study reported the exact number of teeth affected in each patient. The authors of 1 study reported that gingival photographs from frontal and side views were taken at each visit for documentation.[15]

Intervention/Comparison

The effect of systemic AZM on GO was assessed. The medication, potentially causing GO (CsA), remained unchanged throughout the studies.[2,11-15] Other medications, including nifedipine, amlodipine, azathioprine, isradipine, diltiazem, prednisone, and phenytoin, remained unchanged as well.[2,11,12,14,15]

The administration and dosage regimen of AZM varied among the studies. The majority of the studies administered AZM for 3 days, with a daily dosage of 500 mg.[2,11,12,14] In the remaining studies, 500 mg/day for

Table I. Characteristics of the studies included

Author (year)	*Number of patients age range (mean ± SD) ethnicity (number of patients) country number of teeth*	*Follow-up (months)*	*Methods for OH control (number of patients)*	*Gingival surgery (number of patients)*	*Dosage/regimen of AZM*	*Medication potentially causing GO*	*Interruption of medication*	*Adverse events*
Gómez et al. (1997)[12]	31 (17 female) 25−72 years (48 ± 11) n.r. Spain n.r.	6	OH instruction, OH classification in good (19) and poor (12)	No surgery	500 mg/day for 3 days	CsA + prednisone Others‖: Azathioprine, amlodipine, nifedipine, phenytoin	-	-
Jucglà et al. (1998)[13]	15 (6 female) 23−61 years (44) n.r. Spain n.r.	6	Professional tooth cleaning in 10 patients after GO reduction of 50%	No surgery (9), gingivectomy (4)†	500 mg/day for 1 day + 250 mg/day for 4 days	CsA	-	-
Wirnsberger et al. (1998)[14]	24 (9 female) 33−54 years n.r. Austria n.r.	12	OH instruction, OH classification in good and poor	No surgery (9), gingivectomy (15)†	500 mg/day for 3 days	CsA + prednisone Others‖: Amlodipine, diltiazem, isradipine, nifedipine	-	-
Worm et al. (2004)[11]	11 (3 female) 32−55 years (44 ± 7) n.r. Austria n.r.	12	n.r.	Gingivectomy‡	500 mg/day for 3 days	CsA + prednisone	-	n.r.
Chand et al. (2004)[15]	11* (3 female) 3−33 years (17 ± 8) Caucasian (8), African American (1), other (2) USA n.r.	6	n.r.	No surgery	10 mg/kg (max. 500 mg) for 1 day + 5 mg/kg (max. 250 mg) for 4 days	CsA Others‖: Amlodipine, nifedipine	-	-
Tokgöz et al. (2004)[2]	12 (1 female) 24−51 years (35 ± 8) n.r. Turkey n.r.	6	OH classification in good (0), moderate (3), and poor (9)	No surgery (11), gingival surgery (1)§	500 mg/day for 3 days	CsA Others‖: Calcium-channel inhibitors	-	-

*Number of patients adds up to 25 patients when second group is considered.
†Patients with gingivectomy performed prior entry into the study.
‡AZM intake subsequently after gingivectomy.
§Time between gingival surgery and AZM intake not reported.
‖Some patients with intake of at least one additional medication.
AZM, azithromycin; *CEJ,* cementoenamel junction; *CsA,* cyclosporine A; *GO,* gingival overgrowth; *OH,* oral hygiene; n.r., not reported; *SD,* standard deviation.

Table II. Criteria of GO assessment and GO degree at baseline and after 3, 6, and 12 months

Author (year)	*Criteria of GO assessment*		*GO degree*				*Benefit of AZM on GO reduction*
			At baseline	*After 3 months*	*After 6 months*	*After 12 months*	
			Number of patients				
Gómez et al. (1997)[12]	Severe:	Covering two-thirds of crown, or whole attached gingiva affected	11	1*	0	-	+
	Moderate:	Extending to one-half of crown	17	1	0	-	
	Mild:	Thickening of marginal gingiva	3	15	7	-	
	No:	No overgrowth	0	14	23	-	
Jucglà et al. (1998)[13]	Severe:	Covering two-thirds of crown, or whole attached gingiva affected	5	-	-	-	+
	Moderate:	Extending to one-half of crown, or attached gingiva affected localized	7	-	-	-	
	Mild:	Thickening of marginal gingiva, covering one-third of crown	3	-	-	-	
	No:	No overgrowth	0	5	7	-	
	Non-response:	Improvement not sufficient to change the category	-	3	1	-	
	Partial response:	Diminution of at least one category from baseline	-	7	6	-	
	Relapse:	New development of GO after complete response	-	0	1	-	
Wirnsberger et al. (1998)[14]	Severe:	Covering two-thirds of crown, or PP with PPD 4 mm or greater	8†, 4‡	0	0	0	+
	Moderate:	Extending to one-half of crown without PP	4†, 4‡	2†	1†	2†	
	Mild:	Thickening of marginal gingiva, covering one-third of crown or less	3†, 1‡	6†, 2‡	4†, 1‡	4†, 1‡	
	No:	No overgrowth	0	7†, 7‡	10†, 8‡	9†, 8‡	
Worm et al. (2004)[11]	Severe:	Covering two-thirds of crown, or PP with PPD 4 mm or greater	5	-	0	1	+
	Moderate:	Extending to one-half of crown without PP	4	-	1	1	
	Mild:	Thickening of marginal gingiva, covering one-third of crown or less	2	-	3	3	
	No:	No overgrowth	0	-	7	6	
			Mean (mm) ± SE				
Chand et al.(2004)[15]	Measurement of gingival sulcus depth relative to CEJ, summed for each tooth (mesial, distal and buccal sites) and then averaged among all teeth of all patients		12.87 ± 0.40	11.44 ± 0.28	11.41 ± 0.34	-	+
Tokgöz et al. (2004)[2]	Measurement of gingival sulcus depth to CEJ		2.5 ± 0.8	1.5 ± 0.6	1.5 ± 0.5	-	+

*Excluded after 3 months as surgery was performed.
†Patients with gingivectomy performed prior entry into the study.
‡Patients without gingivectomy prior entry into the study.
+, benefit of AZM intake on GO reduction present; *AZM,* azithromycin; *CEJ,* cementoenamel junction; *GO,* gingival overgrowth; *PP,* pseudo-pockets; *PPD,* probing pocket depth; *SE,* standard error.

Table III. Quality assessment of included studies according to Moga et al.[17]

Major components	*Gómez et al. (1997)*[12]	*Jucglà et al. (1998)*[13]	*Wirnsberger et al. (1998)*[14]	*Worm et al. (2004)*[11]	*Chand et al. (2004)*[15]	*Tokgöz et al. (2004)*[2]
Is the hypothesis/aim/objective of the study clearly stated?	+	+	+	+	+	+
Are the characteristics of the participants included in the study described?	+	+	+	+	+	+
Were the cases collected in more than one center?	-	-	-	-	+	-
Are the eligibility criteria (i.e., inclusion and exclusion criteria) for entry into the study clearly stated?	*P*	-	*P*	*P*	*P*	*P*
Were participants recruited consecutively?	+	+	U	+	U	U
Did participants enter the study at a similar point in the disease?	U	-	U	U	U	U
Was the intervention of interest clearly described?	+	+	+	+	+	+
Were additional interventions (co-interventions) reported in the study?	+	+	+	+	+	U
Are the outcome measures established a priori?	+	+	+	+	+	+
Were the relevant outcomes measured with appropriate objective and/or subjective methods?	+	+	+	+	+	+
Were the relevant outcomes measured before and after the intervention?	+	+	+	+	+	+
Were the statistical tests used to assess the relevant outcomes appropriate?	+	+	+	+	+	+
Was the length of follow-up reported?	+	+	+	+	+	+
Was the loss to follow-up reported?	+	+	+	+	+	+
Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	+	-	+	+	+	+
Are the adverse events related with the intervention reported?	+	+	+	-	+	+
Are the conclusions of the study supported by results?	+	+	+	+	+	+
Are both competing interests and sources of support for the study reported?	-	-	-	+	-	-
Percentage of positively graded items	78%	72%	72%	78%	78%	67%

+, yes; -, no; *P*, partially reported; *U,* unclear.

the first day and 250 mg/day for the following 4 days[13] or 10 mg/kg bodyweight (maximum 500 mg) for the first day and 5 mg/kg bodyweight (maximum 250 mg) for the following 4 days[15] were administered. Azithromycin was administered for 1 cycle in 5 studies.[2,11,13-15] In 1 study, 3 patients received a second course of systemic treatment with AZM.[12] A second group (i.e., with intake of systemic metronidazole) was applied in 1 trial.[15]

In 1 study, 10 patients underwent professional tooth cleaning after reduction of GO by 50%.[13] In 2 studies, patients were motivated to brush their teeth properly,[12,14] and 3 studies did not report any methods for improvement of oral hygiene.[2,11,15]

Patients underwent periodontal surgery (i.e., gingivectomy) and were subsequently treated with AZM in one trial.[11] Two studies reported on gingivectomy performed before the start of the study.[13,14]

Outcome

No study reported on blinding of examiners at follow-up. In all included studies, a beneficial effect of systemically administered AZM in terms of reduction of GO was documented (see Table II). A complete resolution of GO was reported for the majority of included patients—that is, 7 of 15 patients,[13] 18 of 24 patients,[14] 7 of 11 patients,[11] and 23 of 31 patients,[12] had no GO anymore 6 months after AZM intake. In one remaining study, mean distance of the gingival sulcus depth to the cementoenamel junction was calculated and was found to have improved by 1 mm, from 2.5 ± 0.8 mm at baseline to 1.5 ± 0.5 mm, after 6 months.[2] In the sixth study, the gingival sulcus depth relative to the cementoenamel junction, recorded at the mesial, distal, and buccal tooth sites, was summed for each tooth and then averaged among

all teeth of all patients.[15] In AZM-treated patients, the resulting mean values changed from 12.87 ± 0.4 mm to 11.41 ± 0.34 mm after 6 months. Two studies reported data after 12 months.[11,14] The results were nearly similar, compared with the 6-month data (i.e., 17 of 24 patients[14] and 6 of 11 patients[11] showed no GO). In 1 study, oral hygiene was suggested to have influenced the reduction of GO—that is, 50% of patients with poor oral hygiene at baseline and 90% of patients with good oral hygiene at baseline had no GO anymore after 6 months.[12]

Quality assessment

The assessment of risk of bias of the included case series is described in Table III and was based on the checklist from Moga et al.[17] to evaluate the methodologic and reporting quality of case series. At least 67% of items relevant for quality assessment were considered in all of the included studies. No study fulfilled all items for control of bias—that is, the risk of bias could not be completely minimized in the included case series.

The objective of the study and the characteristics of the participants included were described in all case series. All case series, except one,[15] were conducted in 1 center, and recruitment of participants were consecutively performed in at least 3 case series.[11-13] Five studies stated exclusion criteria,[2,11,12,14,15] and 1 case series did not provide detailed eligibility criteria.[13] All case series clearly reported the intervention (i.e., administration and dosage regimen of AZM) and defined the primary outcome—that is, GO and the measurement applied—at baseline. In addition, follow-up time and loss to follow-up were consistently stated. Five of 6 case series reported on the occurrence of adverse events related to the intake of AZM.[2,12-15]

DISCUSSION

The aim of this systematic review was to explore the effects of systemically administered AZM on GO. Although GO was induced by CsA in renal transplant recipients, the 6 studies included differed in terms of study population, sample size, additional primary medication, control for oral hygiene, dosage of AZM, gingivectomy performed in some patients, measurement and classification of GO and statistical methods applied.[2,11-15] The pronounced heterogeneity among the studies prohibited conventional statistical meta-analysis. However, all of the 6 included studies,[2,11-15] summarizing data from 104 patients with AZM intake, revealed a beneficial effect of AZM for the parameter "reduction of GO." The summarized data from this systematic review may, therefore, generate an increase of available external evidence.

However, some aspects of the included publications need to be discussed:

1. The number of patients with AZM intake in the studies included, ranged from 11 to 24,[2,11,13-15] and 1 study reported on 31 patients.[12] These are relatively small groups. However, the data available showed consistency among the results of the studies—that is, all of them reported a benefit of systemic AZM intake on the resolution of GO in patients with CsA medication.[2,11-15]
2. The included studies applied different treatment protocols for AZM—that is, 500 mg/day for 3 days,[2,11,12,14] 500 mg for the first day and then 250 mg/day for another 4 days,[13] or 10 mg/kg bodyweight (maximum 500 mg) for the first day and 5 mg/kg bodyweight (maximum 250 mg) for the following 4 days.[15] Azithromycin was well tolerated and did not cause any side effects, although it was combined with various other medications in some cases.[2,11,12,14,15] The different treatment protocols led to similar results in the studies included.[2,11-15] Thus, there might be reason to conclude that these differences in the application protocol did not lead to marked differences in terms of reduction of GO. However, the aspects need further evaluation with clinical trials with larger sample sizes.
3. In addition to AZM and CsA, azathioprine, nifedipine, amlodipine, diltiazem, isradipine, not further specified calcium-channel blocking agents,[2] prednisone[11,12,14] and phenytoin,[12] were administered to some patients to avoid rejection of the renal transplants[11,12,14,15] or for different other medical reasons. These drugs may interact with each other and/or may have an impact on the effect of systemically administered AZM in renal transplant recipients with CsA-induced GO.
4. Oral hygiene is an important confounder for the development of GO in patients with systemic AZM intake.[19,20] In 3 studies from this systematic review, oral hygiene was assessed at baseline.[2,12,14] Additionally, the authors of 2 studies motivated their patients to brush properly.[12,14] After AZM intake, professional tooth cleaning was performed in patients with a reduction of GO of 50% in 1 study.[13] Two studies did not report any methods for control of oral hygiene.[11,15] Although plaque accumulation was considered essential for initiation of drug-induced GO by some authors,[17,19] other authors questioned the importance of oral hygiene.[5,21] However, poor oral hygiene does not seem to be the only cause of GO because several patients with good oral hygiene presented with marked GO.[12]

Dental plaque induces gingival inflammation and may contribute to an exacerbation of CsA-induced GO.[19,22,23] Future studies need to evaluate how CsA-induced GO interacts with different levels of oral hygiene and simultaneous administration of systemic AZM. However, ethical questions need to be considered for this kind of research.

5. Recently, drug-induced GO was described by Murakami et al.[1] in a review of the new classification of periodontal and peri-implant diseases and conditions. GO beginning at the gingival papilla and extending to the marginal and attached gingiva was classified as mild, moderate, and severe gingival enlargement.[1,24] In the studies included in this systematic review, GO was defined using different measures (i.e., previously published scores[11-14] according to Pernu et al.[3,18]) or by measurements in millimeters.[2,15] Data from studies using scores demonstrated a complete resolution of GO 6 months after AZM intake—that is, in 7 of 15 patients,[13] 18 of 24 patients,[14] 7 of 11 patients,[11] and 23 of 31 patients.[12] Such an endpoint was not reported in studies using a millimeter scale.[2,15]

The data from this review are promising and suggest a beneficial effect of systemically administered AZM with respect to the reduction of GO. However, the following parameters are suggested for consideration in future research:

1. Evaluation of systemic AZM with respect to long-term data (>12 months)
2. Comparison of adjunctive systemic AZM to surgical therapy with respect to long-term data (>12 months)
3. Definition of the optimal starting point of the systemic AZM medication
4. Use of relevant outcome parameters, such as a millimeter scale graded to define GO
5. Control of possible confounders, including oral hygiene

CONCLUSIONS

In summary, a limited number of studies in different populations showed the beneficial effect of systemically administered AZM on CsA-induced GO in renal transplant recipients. Azithromycin therapy should be considered as a potential alternative to conventional surgery or at least as a supporting cotherapy. In addition, if AZM is considered as an adjunct to periodontal therapy, a close consultation with a physician is suggested with respect to side effects of AZM.[25]

DISCLOSURE

Parts of this research were conducted by Matthias D. Fuchs in partial fulfillment of the requirements for an MD degree from the University of Basel, Switzerland.

PRESENTATION

Some aspects of this work were presented as a poster (Mendes S, Fuchs MD, Buset SL, Weiger R, Walter C. Does systemically administered azithromycin affects gingival overgrowth? A systematic review on human clinical trials. Europerio9, June 20−23, 2018, Amsterdam, Netherlands; *J Clin Periodontol.* 2018; 45:164, Abstract ID: #787).

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Appendix S1. Electronic search strategy for the database Cochrane Library

No.	*Search syntax*	*Search results*
# 1	MeSH descriptor: [Gingival Overgrowth] explode all trees	65
# 2	MeSH descriptor: [Periodontal Diseases] explode all trees	5667
# 3	MeSH descriptor: [Periodontitis] in all MeSH products	2599
# 4	(Azithromycin) in all text	2116
# 5	#1 AND #4	6
# 6	#2 AND #4	52
# 7	#3 AND #4	42
# 8	#5 OR #6 OR #7	52

Appendix S2. Criteria for assessing the methodological and reporting quality of case series studies according to Moga et al.[17]

Major Components	*Judgment*
1. Is the hypothesis/aim/objective of the study clearly stated?	Yes, Unclear, No
2. Are the characteristics of the participants included in the study described?	Yes, Partially reported, No
3. Were the cases collected in more than one centre?	Yes, Unclear, No
4. Are the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Yes, Partially reported, No
5. Were participants recruited consecutively?	Yes, Unclear, No
6. Did participants enter the study at a similar point in the disease?	Yes, Unclear, No
7. Was the intervention of interest clearly described?	Yes, Partially reported, No
8. Were additional interventions (co-interventions) reported in the study?	Yes, Unclear, No
9. Are the outcome measures established a priori?	Yes, Partially reported, No
10. Were the relevant outcomes measured with appropriate objective and/or subjective methods?	Yes, Unclear, No
11. Were the relevant outcomes measured before and after the intervention?	Yes, Unclear, No
12. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes, Unclear, No
13. Was the length of follow-up reported?	Yes, Unclear, No
14. Was the loss to follow-up reported?	Yes, Unclear, No
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	Yes, Unclear or partially reported, No
16. Are the adverse events related with the intervention reported?	Yes, Partially reported, No
17. Are the conclusions of the study supported by results?	Yes, Partially reported, No
18. Are both competing interests and sources of support for the study reported?	Yes, Partially reported, No

Appendix S3. Studies excluded based on full-text analysis, and reasons for exclusion

First author (year of publication)	*Reason for exclusion*
Boran et al. (1996)[26]	1
Citterio et al. (2001)[27]	2
Kim et al. (2008)[28]	3
Kwun et al. (2003)[29]	4
Mesa et al. (2003)[30]	1
Nafar et al. (2003)[31]	4
Nash et al. (1998)[32]	1
Palomar et al. (1998)[33]	1
Puig et al. (1997)[34]	1
Ramalho et al. (2007)[35]	1

1, follow-up time < 6 months; 2, no quantification of GO; 3, *ex vivo* study; 4, number of patients < 10.