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REVIEW

Non-surgical periodontal therapy supplemented with systemically administered azithromycin: a systematic review of RCTs

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Abstract
Background Azithromycin may be an alternative adjunctive systemic antibiotic in non-surgical periodontal therapy.
Objective This study aims to identify randomized controlled trials evaluating non-surgical periodontal treatment of chronic and/or aggressive periodontitis supplemented with systemically administered azithromycin.
Materials and methods A systematic literature search was performed for publications published by 31 March 2014 using electronic databases and hand search. Randomized controlled trials published in English or German language, with a follow-up ≥6 months were included. From 231 titles identified, nine publications were eligible for inclusion.
Results Among the studies included, showing some risk of bias, seven reported on patients with chronic periodontitis and two with aggressive periodontitis. Minor adverse events were described in five studies. A synthesis of results using a vote counting method was applied. Significant ($p<0.05$) beneficial effects of azithromycin were shown in six studies for probing depth changes and in five studies for clinical attachment level changes.
Conclusion In contrast to aggressive periodontitis patients, data from this analysis indicate a potential benefit of systemic azithromycin as adjunctive to non-surgical periodontal therapy in chronic periodontitis patients.
Clinical relevance When contraindications for the standard antibiotics are present, azithromycin (AZM) may be considered as alternative systemically administered antibiotic drug in selected cases of chronic periodontitis.

Keywords Periodontal debridement · Azithromycin · Aggressive periodontitis · Chronic periodontitis

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Introduction

Recent reviews document the benefit of systemic antibiotics as an adjunct to scaling and root planing (SRP), particularly the combination of amoxicillin and metronidazole [1–5]. The combination of metronidazole and amoxicillin is highly active against the suspected bacterial spectrum of the pathogenic periodontal microflora [6–8]. While early reports suggest a synergistic mode of action against *Aggregatibacter* (*Actinobacillus*) *actinomycetemcomitans* (e.g. [9, 10]), recent data show a primarily combinatorial effect [7, 8]. The combination of the two systemic antibiotics has been frequently prescribed as an integral part in non-surgical therapy for aggressive forms of periodontitis [11–14]. Further, the use of metronidazole plus amoxicillin as an adjunct to SRP in periodontitis patients was suggested in severe chronic periodontitis (ChP) [15, 16], in periodontitis among smokers (*smokers' periodontitis*) [17, 18], in severely medically compromised patients [19], in periodontitis associated with the use of bisphosphonates [20], or to reduce the need for further periodontal surgery [21]. In the late 1980s, the combination of amoxicillin and metronidazole was introduced [22] as an adjunct to SRP in non-surgical periodontal therapy for periodontitis associated with *A.* (*A.*) *actinomycetemcomitans*. In this early report, a dosage of 250 mg metronidazole and 375 mg amoxicillin three times a day for 7 days was applied and

suggested to be administered at the day of instrumentation, e.g. after instrumentation of the last quadrant [2]. Currently, rather different protocols regarding dosage and duration were reported [23–25] for different reasons, including nationally specified administrations or dose adaptation according to body weight of the patient.

However, this adjunctive antibiotic drug application remains a field for controversies [26–29]:

(i) While systemic antibiotics are particularly indicated in combination with subgingival biofilm management, the major concern when administering antibiotic medication is the presence or possible development of antibiotic resistance and/or other severe complications including cardiovascular events [29–31]. Antibiotic resistance increases dramatically worldwide [32], thus highlighting the need for a careful assessment of its indications, duration and dosage.
(ii) In addition, a wide range of adverse drug reactions have been reported for the combination of amoxicillin and metronidazole [2, 33].
(iii) Dosage regime and patient's adherence contribute to the effectiveness and resistance of antibiotic agents [34]. In particular, the frequency of intake and duration of amoxicillin prescription ≥7 days led to significantly reduced compliance [35].

Therefore, an ongoing search for suitable alternatives as adjunctive to non-surgical periodontal therapy is reasonable. Recently, a review on azithromycin (AZM), a broad-spectrum, second-generation macrolide, was published [36]. Its promising pharmacokinetic qualities include the uptake in neutrophil granulocytes and fibroblasts, a higher concentration in tissue than in plasma, a slow release at the site of infection and a low incidence of adverse events [37–39]. Its long half-life in plasma (93±70 h) and granulocytes (210± 69 h) enables single dosages per day and a short administration time [40].

While recent reviews analyzed the effects of systemic antibiotics more broadly and generally [3–5], the specific aim of this systematic review was to evaluate randomized controlled trials (RCTs) analyzing the effect and/or relevant parameters for effect modification of systemically administered AZM as an adjuvant to SRP in non-surgical periodontal therapy.

Methods

Protocols

The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria [41, 42] (Appendix 1). The research question was explored using the population, intervention, comparison and outcomes (PICO) method.

The specific question addressed was as follows:

In patients suffering from periodontitis (P), does systemically administered AZM adjunctive to SRP during periodontal non-surgical therapy (I) have a beneficial effect on clinical periodontal parameters after ≥6 months of observation (O) compared to SRP with placebo or without adjunctive antibiotic medication (C)?

Search strategy

The electronic bibliographic databases MEDLINE, EMBASE and Cochrane Library were searched for citations included as of 31 March 2014. Unpublished reports were identified by searching the OpenGrey (formerly OpenSIGLE) database that lists unpublished literature (http://www.opengrey.eu/). These searches were supplemented by hand searching of pertinent journals. Additionally, potentially relevant citations were harvested from the bibliographies of reports examined for inclusion eligibility. The search protocols within the different databases were applied and validated as identically as possible. Combinations of the validated search terms for MEDLINE/PubMed, EMBASE and Cochrane Library were "periodontal diseases" AND "azithromycin".

Review process

Two of the authors (SB and CW) screened the titles for potential eligibility according to the inclusion criteria. Based on the abstract screening, 14 studies were selected for full text retrieval and review. Discrepancies in scores allocated to publications were discussed among the authors until a consensus was reached.

Inclusion criteria

The search was limited to RCTs investigating the effects of systemically administered AZM on non-surgical periodontal therapy. Inclusion criteria were the following: publication in German or English language, human clinical trials, diagnosis of aggressive and/or chronic periodontitis, non-surgical periodontal treatment, systemic administration of AZM, follow-up of at least 6 months, clinical periodontal outcome parameters [tooth loss, probing depth (PD) and/or clinical attachment level (CAL)] and a control group with non-surgical periodontal treatment with or without placebo.

Exclusion criteria

Studies were excluded for the following reasons: local AZM administration, surgical periodontal treatment, peri-

implantitis/peri-mucositis therapy, treatment of gingival overgrowth and reviews or case reports.

Outcome measures

The primary outcome measure was tooth loss after non-surgical periodontal treatment supplemented with or without systemically administered AZM. Changes in PD, CAL and minor/major adverse events were evaluated as secondary outcome variables.

Data extraction

Demographic data, sample size, definition of periodontal disease, measurement of periodontal disease (PD and/or CAL and recording protocol, i.e. full mouth or partial mouth), definition and description of tobacco use, dosage and administration regime of AZM, minor adverse events (e.g. gastrointestinal tract reactions such as diarrhoea, nausea, abdominal pain or vomiting; peripheral nervous system reactions, such as headache or dizziness [43]) and major adverse events (e.g. hepatotoxicity [44]) and the effect of AZM on clinical periodontal parameters as outcome variables were extracted and summarized in Tables 1, 2 and 3.

Extent (e.g. localized/generalized; proportion of sites/teeth affected) and severity (e.g. mild, moderate or severe) of periodontal disease were reported using various summary measures. Effect of adjunctive AZM was expressed as mean PD or CAL, mean change in PD or CAL or percentage of teeth with change in PD or CAL ≥1 mm.

Risk of bias

The included studies were evaluated using the Cochrane Collaboration's tool for assessing risk of bias [45] (Appendix 2). Considering the adequacy of the reporting in the respective studies, the items were graded and the percentage of positively graded items was calculated [46].

Summary measure

Due to the pronounced heterogeneity with respect to treatment protocol and outcome measures, as well as variation in study population, sample size and/or statistical methods, a synthesis of the evidence of the included studies using a vote counting method was applied (http://handbook.cochrane.org/chapter_9/9_4_11_use_of_vote_counting_for_meta_analysis.htm).

Results

Study selection

Initially, 231 titles were identified by electronic and hand searches (Fig. 1). Titles were screened by two reviewers (kappa=0.759). Full text analysis of the 14 potentially eligible reports led to exclusion of five further studies (Appendix 4). Subsequently, nine reports published between 2005 and 2012 fulfilled the inclusion criteria and revealed a moderate to low risk of bias (Appendix 2). In six of the nine studies, 84 % of the possible items (sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, other sources of bias) were considered. The remaining three studies valued at least two of six items. Tooth loss was considered as an outcome in one study [48]. All included studies reported on PD and CAL.

Summary of studies: characteristics (PICO)

Population

Clinical trials comprised 338 participants with 142 women. Studies included a minimum of 24 [47] up to 92 [48] subjects with mean ages ranging from 20 to 51 years [47, 49].

Intervention/comparison

Two of the nine studies assessed the effect of adjunctive AZM in distinct population groups with respect to the presence of *Porphyromonas gingivalis* [50] and smoking [51]. From the nine trials included, two investigated a population with aggressive periodontitis (AgP) [47, 52]. Seven publications considered subjects suffering from ChP [48–51, 53–55]. Full-mouth recording (FMR) using measurements up to six sites per tooth was performed in all studies to assess periodontal disease [47–55] (Appendix 3).

The administration of AZM and the sequence of non-surgical periodontal therapy varied among the studies. The majority of studies applied quadrant- or sextant-wise SRP weekly or within 2–3 weeks or two to six sessions within 1–2 weeks. Full-mouth SRP in one visit was applied in two studies [49, 53]. AZM was subscribed at the first [47, 48] or last [50–52, 54, 55] session or 3 days prior [49, 53] to the start of mechanical instrumentation (Table 3).

Seven publications prescribed AZM with a dosage of 500 mg once daily for 3 days [47–50, 52–54]. In one publication, 500 mg AZM was administered for 5 days [55], and another trial prescribed 500 mg AZM on the first and 250 mg once daily on the 2nd to the 5th day [51] (Table 3).

A placebo medication was used in the control groups in five studies [47, 50, 52, 54, 55]. In one study, AZM was compared to further adjunctive antibiotic medications, while

Table 1 Results: probing depth (PD) as an outcome variable

Author (year)	Number, age, population, country	Adjustment	Outcome		Adjunctive effect of AZM
			6 months	12 months	
Chronic periodontitis					
Gomi et al. (2007) [53]	34, AZM = 45.4±14.3, C=51.0±8.8, n.r., Japan	n.r.	Mean PD[a]: AZM: 2.36±0.76 mm, C:3.30±0.36 mm, $p<0.001$		+
Haffajee et al. (2007) [48]	92, AZM = 47±14, SRP=43±15, n.r., USA	Baseline values	Significant differences in PD change in initially deep (>6 mm) sites in AZM group compared to the control group	Significant differences in PD change in initially deep (>6 mm) sites in AZM group compared to the control group	+
Han et al. (2012) [54]	28, AZM = 46.8±5.1, C[b]=44.8±5.0, n.r., Turkey	Baseline values	No significant difference between AZM and control group[b] Reduction in mean PD AZM: 1.81±0.5, C[b]: 1.66±0.5 %sites converting from ≥7 to <4 mm AZM: 79.33±24.7, C[b]: 57.56±30.5		−
Mascarenhas et al. (2005) [51]	30, AZM = 47±10.06 (33–64), C=45.34±10.75 (31–66), smokers, USA	n.r.	No significant difference in mean change in per-patient PD in shallow sites (1–3 mm) between AZM and control group Mean change in per-patient PD in moderate sites (4–6 mm) AZM: 1.7 mm, C: 1.0 mm, $p<0.05$ Mean change in per-patient PD in deep sites (≥6 mm) AZM: 3.52 mm, C: 1.98 mm, $p<0.05$		+
Oteo et al. (2010) [50]	28[c, d], AZM = 15, 46.6 (38–62), C[b]=13, 47.1 (36–62), *P. gingivalis*, Spain	Baseline values, smoking gender	Significant difference in reduction in mean PD ($p=0.009$) AZM: 0.78, SE=0.09, 95 % CI=0.59–0.97 C[b]: 0.38, SE=0.11, 95 % CI=0.16–0.60 Significant difference in reduction in mean ‰ PD 4–6 mm ($p=0.003$) AZM: 0.20, SE=0.02, 95 % CI=0.17–0.24 C[b]: 0.11, SE=0.02, 95 % CI=0.06–0.15		+
Sampaio et al. (2011) [55]	40, AZM = 44.40±7.42, C[b]=43.52±5.90, n.r., Brazil	n.r.	Changes in mean full-mouth PD AZM: −1.54±1.62, C[b]: −1.71±1.71, $p>0.05$ Changes in mean PD in sites with PD 4–6 mm AZM: −1.66±1.01, C[b]: −1.67±1.00, $p>0.05$ Changes in mean PD in sites with PD ≥7 mm AZM: −3.56±1.54, C[b]: −3.65±1.78, $p>0.05$ Mean PD AZM: 3.24±0.41 mm, C[b]: 3.36±0.38 mm, $p>0.05$	Changes in mean full-mouth PD AZM: −1.41±1.68, C[b]: −1.77±1.80, $p>0.05$ Changes in mean in sites with PD 4-6 mm AZM: −1.14±1.16, C[b]: −1.74±1.02, $p>0.05$ Changes in mean PD in sites with PD ≥7 mm AZM: −3.45±1.74, C[b]: −3.83±1.92, $p>0.05$ Mean PD AZM: 3.36±0.44 mm, C[b]: 3.34±0.50 mm, $p>0.05$	−
Yashima et al. (2009) [49]	30, T1=51.1±11.6, T2=50.8±14.2, C=51.0±10.6, n.r., Japan	n.r.	Reduction in PD in T1 (full-mouth SRP) versus C and T2 (SRP in 3 sessions within 1 week) versus C at all time points ($p<0.001$, $p<0.005$)	Reduction in PD in T1 versus C and T2 versus C at all time points ($p<0.001$, $p<0.005$)	+
Aggressive periodontitis					
Emingil et al. (2012) [52]	32, AZM = 28.75±4.4, C[b]=29.56±5.9, n.r., Turkey	n.r.	PD 4–6 mm AZM: 95 % CI=2.67–2.33, C[b]: 95 % CI=2.57–2.23, $p=0.632$		−

Table 1 (continued)

Author (year)	Number, age, population, country	Adjustment	Outcome		Adjunctive effect of AZM
			6 months	12 months	
			PD ≥7 mm AZM: 95 % CI=3.48–2.86, C[b]: 95 % CI=3.38–2.84, p=0.608		
Haas et al. (2008) [47]	24[e, f], AZM = 22.5±3.6, C[b]=20.1±3.6, n.r., Brazil	n.r.	n.r.	Mean changes in PD in sites with PD 4–6 mm AZM: 2.02±0.14 mm, C[b]: 1.25±0.17 mm, p=0.003 Mean changes in PD in sites with PD ≥7 mm AZM: 3.49±0.23, C[b]: 2.76±0.51, p=0.21 Mean changes in PD in sites with PD ≥4 mm AZM: 2.88±0.23 mm, C[b]: 1.85±0.36 mm, p=0.025 %teeth PD decrease ≥2 mm AZM: 81.34±4.00, C[b]: 57.85±8.21, p=0.017 %teeth PD increase ≥1 mm AZM: 0, C[b]: 4.13±1.40, p=0.007	+

PD probing depth, *C* control, *AZM* azithromycin, *SRP* scaling and root planing, *SE* standard error, *CI* confidence interval, *n.r.* not reported

[a] Follow-up of 6.25 months

[b] Placebo

[c] Exclusion of severe chronic periodontitis [≥1 tooth per quadrant PD >7 mm (except if scheduled for extraction)]

[d] Stratified for smoking status

[e] Only teeth presenting CAL or PD ≥4 mm at baseline were considered in analyses of changes in CAL, PD and BoP

[f] Groups stratified for smoking status and disease extent before randomization

Table 2 Results: clinical attachment level (CAL) as an outcome variable

Author and year	Number, age, population, country	Adjustment	Outcome		Adjunctive effect of AZM
			6 months	12 months	
Chronic periodontitis					
Gomi et al. (2007) [53]	34, AZM = 45.4±14.3, C=51.0±8.8, n.r., Japan	n.r.	No significant difference in mean CAL[a] AZM: 4.85±1.05 mm, C: 5.74±0.96 mm		−
Haffajee et al. (2007) [48]	92, AZM = 47±14, SRP=43±15, n.r., USA	Baseline values	Significant differences in CAL gain in initially deep (>6 mm) sites in AZM group compared to the control group	Significant differences in CAL gain in initially deep (>6 mm) sites in AZM group compared to the control group	+
Han et al. (2012) [54]	28, AZM = 46.8±5.1 C[b]=44.8±5.0, n.r., Turkey	baseline values	No significant difference between AZM and control group[b] Reduction in mean CAL AZM: 1.55±0.5, C[b]: 1.54±0.5		−
Mascarenhas et al. (2005) [51]	30, AZM = 47±10.06 (33–64), C=45.34±10.75 (31–66), smokers, USA	n.r.	No significant difference in mean change in per-patient CAL in shallow sites (1–3 mm) between AZM and control group No significant difference in mean change in per-patient CAL in moderate sites (4–6 mm) between T and C Mean change in per-patient CAL in deep sites (≥6 mm) AZM: 2.56 mm, C: 1.32 mm, $p<0.05$ No significant difference in %sites with ≥2 mm CAL loss AZM: 1.3, C: 1.2, $p>0.05$		+
Oteo et al. (2010) [50]	28[c, d], AZM = 15, 46.6 (38–62); C=13, 47.1 (36–62), *P. gingivalis*, Spain	Baseline values, smoking gender	Significant difference in change in mean CAL AZM: 0.76, SE=0.12, 95 % CI=0.52–1.01 C:0.28, SE=0.14, 95 % CI=0.00–0.57, $p=0.016$		+
Sampaio et al. (2011) [55]	40, AZM = 44.40±7.42, C[b]=43.52±5.9, n.r., Brazil	n.r.	Changes in mean full-mouth CAL AZM: −1.05±1.56, C[b]: −1.05±1.54, $p>0.05$ Changes in mean CAL in sites PD 4–6 mm AZM: −1.18±1.21, C[b]: −1.10±1.25, $p>0.05$ Changes in mean CAL in sites with PD ≥7 mm AZM: −2.62±1.56, C[b]: −2.29±1.56, $p>0.05$ Mean CAL AZM: 4.43±0.81 mm, C[b]: 4.70±0.83 mm, $p>0.05$	Changes in mean full-mouth CAL AZM: −1.02±1.62, C[b]: −1.04±1.65, $p>0.05$ Changes in mean CAL in sites with PD 4–6 mm AZM: −1.14±1.16, C[b]: −1.15±1.31, $p>0.05$ Changes in mean CAL in sites with PD ≥7 mm AZM: −2.68±1.76, C[b]: −2.35±1.70, $p>0.05$ Mean CAL AZM: 4.44±0.77 mm C[b]: 4.69±0.89 mm, $p>0.05$	−
Yashima et al. (2009) [49]	30, T1=51.1±11.6, T2=50.8±14.2, C=51.0±10.6, n.r., Japan	n.r.	Reduction in CAL in T1 (full-mouth SRP) versus C and T2 (SRP in 3 sessions within 1 week) versus C at 6, 9 and 12 months ($p<0.005$)	Reduction in CAL in T1 versus C and T2 versus C at 6, 9 and 12 months ($p<0.005$)	+
Aggressive periodontitis					
Emingil et al. (2012) [52]	32, AZM = 28.75±4.4, C[b]=29.56±5.9, n.r., Turkey	n.r.	CAL AZM: 95 % CI=3.57–4.29, C[b]: 95 % CI=3.35–3.86, $p=0.217$		−

Table 2 (continued)

Author and year	Number, age, population, country	Adjustment	Outcome		Adjunctive effect of AZM
			6 months	12 months	
Haas et al. (2008) [47]	24[e, f], AZM = 22.5±3.6, C[b]=20.1±3.6, n.r., Brazil	n.r.	n.r.	Mean changes in CAL in sites with PD 4–6 mm AZM: 1.21±0.16 mm, C[b]: 0.74±0.28 mm, p=0.16 Mean changes in CAL in sites with PD ≥7 mm AZM: 2.01±0.23 mm, C[b]: 1.35±0.34 mm, p=0.125 Mean changes in CAL in sites with PD ≥4 mm AZM: 1.68±0.20 mm, C[b]: 0.97±0.29 mm, p=0.05 %teeth CAL decrease ≥2 mm AZM: 51.49±7.19, C[b]: 36.36±7.95, p=0.17 %teeth CAL increase ≥1 mm AZM: 2.24±0.97, C[b]: 11.57±3.43, p=0.015	+

CAL clinical attachment loss, *PD* probing depth, *C* control, *AZM* azithromycin, *SRP* scaling and root planing, *SE* standard error, *CI* confidence interval, *n.r.* not reported

[a] Follow-up of 6.25 months

[b] Placebo

[c] Exclusion of severe chronic periodontitis [≥1 tooth per quadrant PD >7 mm (except if scheduled for extraction)]

[d] Stratified for smoking status

[e] Only teeth presenting CAL or PD ≥4 mm at baseline were considered in analyses of changes in CAL, PD and BoP

[f] Groups stratified for smoking status and disease extent before randomization

Table 3 Treatment regime, dosage of azithromycin (AZM) and adverse events of included publications

	Treatment regime	Dosage of AZM (mg)	Adverse events
Chronic periodontitis			
Gomi et al. (2007) [53]	3 days before full-mouth SRP[a]	500–500–500	Diarrhoea
Haffajee et al. (2007) [48]	First session of quadrant-wise SRP in weekly visits	500–500–500	Allergic reaction to AZM, difficulties swallowing the tablets
Han et al. (2012) [54]	Last session of quadrant-wise SRP in sequential sessions within 4 weeks	500–500–500	None
Mascarenhas et al. (2005) [51]	End of last SRP session of 2 sessions within 1 week[b]	500–250–250–250–250	n.r.
Oteo et al. (2010) [50]	End of last SRP session of 2 sessions within 1 week	500–500–500	Diarrhoea
Sampaio et al. (2011) [55]	End of last session, SRP in 4–6 sessions in 2 weeks	500–500–500–500–500	Diarrhoea (2x), headache and dizziness (1x), excessive sleepiness (3x), metallic taste (2x), general unwellness (1x)
Yashima et al. (2009)[c] [49]	3 days before full-mouth SRP 3 days before SRP in 3 sessions within 1 week	500–500–500	Diarrhoea
Aggressive periodontitis			
Emingil et al. (2012) [52]	End of last session of quadrant-wise SRP within 3 weeks	500–500–500	None
Haas et al. (2008) [47]	First session of quadrant- or sextant-wise SRP within 2 weeks	500–500–500	None

SRP scaling and root planing, *n.r.* not reported

[a] Control group: SRP in 4–6 sessions with 1-week intervals

[b] SRP within 1-2 weeks

[c] Control group: SRP in six sessions within 6 weeks

the control received SRP only [48]. From this study [48], only the intervention with AZM and the control were used for comparison in the current review.

Outcomes

Chronic periodontitis Data on tooth loss as an outcome were reported by one study [48]. While no teeth were lost in the control group, two teeth were extracted in the AZM group during the course of the study.

Five out of seven studies investigating ChP documented a beneficial effect of systemically administered AZM compared to SRP in terms of the PD measures applied [48–51, 53] (Table 1). One study reported a significant lower mean PD after 6 months compared to the control group [53]. A significantly higher PD reduction in the test group after 6 months was shown in one study [50]. Two publications described significant differences in PD change between test and control groups at 6 and 12 months [48, 49]. No beneficial effect of AZM was found in two studies [54, 55] (Table 1).

In three of the seven studies on ChP, the changes in CAL differed significantly between test and control groups after 6 months [50] or 12 months [48, 49]. No significant differences in CAL measures were described in three studies [53–55] (Table 2).

One study reported conflicting results on the outcome in smokers with ChP [51]. A significant mean change in per-patient PD was described in moderate and deep sites as well as in mean per-patient CAL in deep sites, when adjunctive AZM was applied. No significant changes were found in mean changes in per-patient PD and CAL in shallow sites or in mean changes in per-patient CAL in moderate sites or percentages of sites with CAL loss ≥2 mm (Tables 1 and 2).

Aggressive periodontitis From the two studies investigating treatment in patients with AgP, one reported a positive effect of AZM revealing a significantly higher percentage of teeth with a PD decrease of ≥2 mm in the test group. With respect to deep sites (PD ≥7 mm), there was, however, no significant difference in mean PD change after 12 months [47] (Table 1). Emingil et al. [52] detected no significant difference in PD measures between the test and placebo group after 6 months [52] (Table 1).

CAL changes differed significantly between test and control in sites with CAL ≥4 mm and in the percentage of teeth with CAL increase of ≥1 mm [47]. Neither the percentage of teeth with CAL decrease ≥2 mm nor the sites with CAL 4–6 and ≥7 mm revealed any difference between test and control [47, 52] (Table 2).

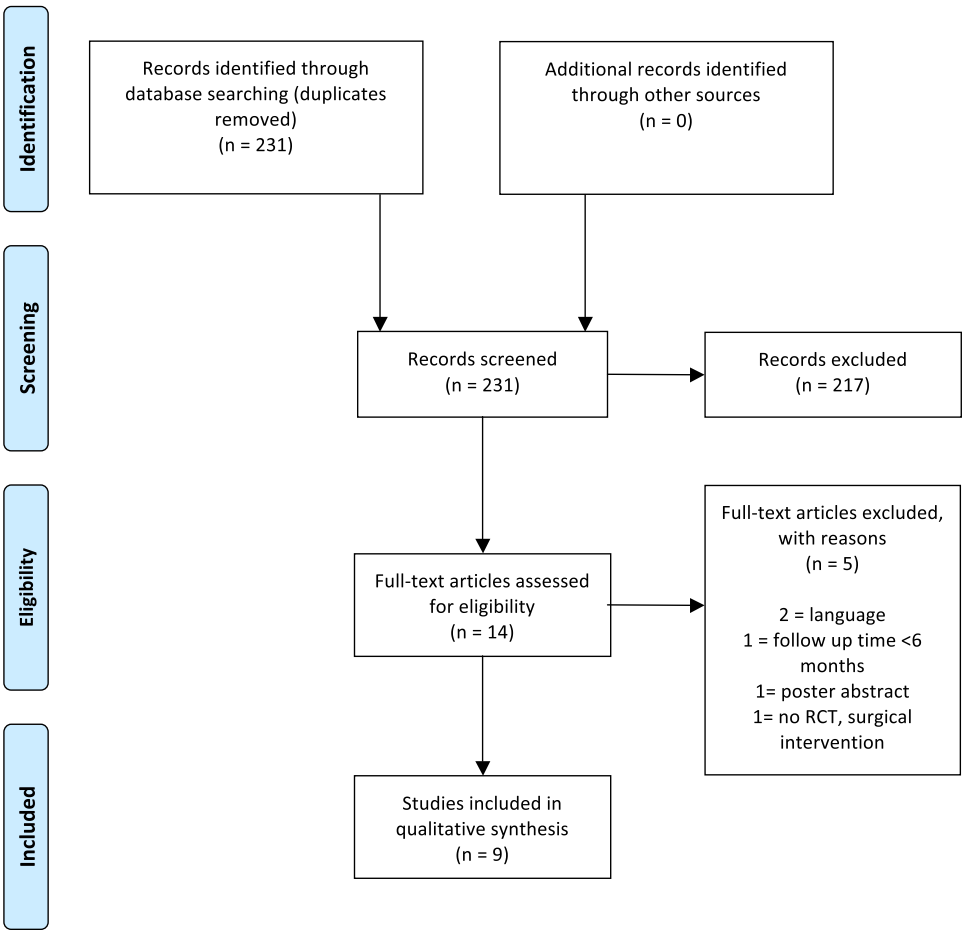

Fig. 1 Selection process for the studies included (from [42]; for more information, visit www.prisma-statement.org)

Adverse events Minor adverse events were reported in five studies such as gastrointestinal reactions (e.g. diarrhoea, metallic taste) [49, 50, 53, 55] or peripheral nervous system reactions (e.g. headache and dizziness) [55]. One study described an allergic reaction [48], but no information on extent or severity was described. None of the included studies reported on major adverse events.

Discussion

The aim of this systematic review was to explore the effect and to discuss the relevant parameters for effect modification of systemically administered AZM on non-surgical periodontal therapy with SRP. The nine RCTs included differed in terms of study population, sample size, risk of bias, statistical methods applied, primary outcome, administration of placebo, start of medication and dosage of AZM and/or sequencing of non-surgical treatment. The pronounced heterogeneity among the studies led to a synthesis of results using a vote counting method applied for the secondary outcome parameters, PD and CAL, while prohibiting a conventional statistical meta-analysis. In addition, the methodological quality of included studies revealed a relative low risk of bias in the majority of included studies (Appendix 2). Keeping these issues in mind, five (PD) and four (CAL) out of seven studies revealed a beneficial effect of AZM for the clinical relevant parameters, PD and CAL, in ChP patients. The two studies describing the outcome in AgP patients documented conflicting results in terms of beneficial effects of AZM as an adjunct to SRP.

Recent reviews indicate significant benefits of several systemic antibiotics, including AZM, in non-surgical treatment of chronic and/or aggressive periodontitis [3–5]. Herrera et al. [3] reviewed a number of RCTs administering local and systemic antibiotics, including two of the seven studies on ChP assessed in this analysis [3]. A broad analysis with a meta-analysis of data from several antibiotic agents, dosage and administration regimes on the effects of systemic antibiotics

in non-surgical periodontitis treatment was performed by Keestra et al. [4, 5]. Our review analyzed the clinical effects from RCTs using systemically administered AZM compared to SRP without adjunctive antibiotic. This approach allowed the observation of differential effects of AZM in the light of mode and/or time point of application (see below). Particularly, the use of adjunctive systemic antibiotics in non-surgical treatment of AgP is well established [4, 11–14]. In our review, only two studies reported on AgP patients and demonstrated conflicting results. While Emingil et al. [52] did not report beneficial effects of AZM, Haas et al. [47] demonstrated a higher change in mean PD in sites with moderate PD (4–6 mm), but not in sites with severe PD of ≥7 mm. These limited data, however, prohibit stating a reliable conclusion to AgP patients.

The included studies applied different treatment protocols for SRP, i.e. SRP in two to six sessions within 1 to 4 weeks [47–52, 54, 55] or full-mouth SRP [49, 53]. However, in terms of PD reduction, the sequences used may be comparable when SRP is applied without systemic antibiotics [56, 57] or in conjunction with AZM [49]. With respect to the possible positive adjunctive effect of AZM, the studies included did not reveal a superiority of any treatment protocol (Tables 1, 2 and 3). In other words, the ideal therapeutic sequencing of SRP with maximal effects of AZM needs to be identified in further RCTs.

The seven studies on ChP applied AZM with 500 mg once daily for 3 days [48–50, 53, 54] to 5 days [55] or applied 500 mg on the 1st day, followed by 250 mg for four further days [51]. An extended period of AZM intake was not associated with a beneficial effect of AZM in comparison to control, while several adverse events, including diarrhoea and sleepiness, were reported by the test group in one study [55].

Minor adverse events were present in five of the nine studies included. In contrast to the combination of amoxicillin and metronidazole, AZM intake is regarded to have very low occurrence of adverse events [58]. However, as mentioned in the "Introduction", a possible cardiovascular risk [31] of AZM intake was raised in the literature. While there are some reports available describing these severe complications, a recent meta-analysis comprising data from 12 RCTs found no increased risks for mortality or for cardiovascular events associated with azithromycin therapy compared with placebo [59]. When AZM is selected as an antibiotic drug in periodontitis therapy particularly in patients with a cardiovascular history, the consultation of the patient's physician is advisable.

As described earlier, the duration of antibiotic intake may have an impact on adherence to the administration protocol. Compared to the standard [1, 2] with amoxicillin and metronidazole administered for at least 7 days, the use of AZM facilitated a shorter and lower dosage regime, which may have the potential to improve patient compliance. A short administration period of only 3 days was recently presented also for the combination of amoxicillin and metronidazole [23].

Further variations were observed in the studies included regarding the start of antibiotic intake. All studies administering AZM 3 days before or at the first SRP visit documented a beneficial effect of AZM [48, 49, 53]. In contrast, among the four studies prescribing AZM at the last session of SRP [50, 51, 54, 55], only two reported a beneficial effect of AZM [50, 51]. This observation might be explained by the pharmacological properties of AZM, particularly the uptake in phagocytic cells and the slow release from these cells [37–39, 60]. Evidence from an analysis of brain tissues indicates an increase of the AZM concentration from the 1st to the 2nd day of intake [61]. For periodontal tissues and gingival crevicular fluid, an elevated concentration of AZM was shown [62, 63]. Therefore, an administration before or at the start of the therapy seems to facilitate a maximum and/or sufficiently high AZM concentration during the performance of SRP [48, 49, 53]. Given the observations from this systematic analysis of RCTs, the treatment regime for adjunctive AZM differs markedly from the protocol for adjunctive amoxicillin and metronidazole. It has been suggested that the combination of amoxicillin and metronidazole "should start on the day of debridement completion", when the biofilm in all affected periodontia is disrupted, i.e. in the case of quadrant-wise SRP after instrumentation of the last quadrant and in the case of full-mouth scaling before the SRP on the same day [2].

A distinction between the outcomes in sites with different PD was given in five studies [47, 50–52, 55]. Certainly, the outcome after SRP of deeper PD is more critical due to the limitations of non-surgical mechanical debridement particularly in multi-rooted teeth [64–66]. Since a residual PD of >5 mm after active treatment is at risk for ongoing attachment loss [67], the number of sites with PD above that threshold is of focused interest in order to have an estimate of sites in need for further (surgical) treatment. Recently, the potential of the combination of amoxicillin and metronidazole for the avoidance of surgical therapy was shown [21].

The healing time allowed to elapse after non-surgical periodontal treatment is of utmost importance for decision-making at a reasonable time point. Evidence shows a marked reduction of PD after SRP after 3 months [68]. However, in initially deep sites, wound healing seems to require more than 3 months [68]. In the current review, only studies with at least 6-month observation period were included to account for the healing time required after non-surgical periodontal therapy. Any longer observation periods are challenging and potentially assess the additional influence of the supportive periodontal treatment and not only the effect of the initial active treatment.

Tobacco consumption is known to have a negative influence on periodontitis progression and treatment outcome [69].

A beneficial effect of adjunctive amoxicillin and metronidazole in non-surgical therapy of tobacco-associated periodontal disease has been described [18]. While one study defined smoking broadly as >10 cigarettes a day and non-smoking as non-smoker, former smoker or zero-to-nine cigarettes a day [50], two publications excluded subjects smoking ≥10 cigarettes a day [52, 54]. Detailed data on tobacco consumption of the patients were missing in four trials [47, 48, 53, 55]. Mascarenhas et al. [51] included only smokers, and Yashima et al. [49] included solely non-smoking participants. Smoking was considered as a confounding factor in the statistical analyses in two studies [47, 50]. Therefore, the distinctive effect of adjunctive AZM in *smokers' periodontitis* could not be explored sufficiently. Since periodontal surgery in smokers needs to be carefully considered due to an increased risk of complications, further research focusing on this clinically relevant and highly prevalent population of periodontitis patients is indicated [69].

The studies included in the current review revealed some variability related to demographic data and study designs. The number of subjects in the majority of studies ranged between 24 and 40, while one study reported on 92 patients allocated to three treatment groups and one control [48]. Although, in most studies, the number of included patients was justified by preceding power calculations [47, 48, 50, 52, 54, 55], one has to be aware that a sample size is strongly related to study quality and risk of bias [70]. Study origin is another factor, which has to be accounted for when interpreting standard of care in conjunction to socioeconomic status, outcomes from antibiotic administration or prevalence of bacterial resistance to antibiotics [28, 29].

Conclusion

In summary, several studies in different populations have explored a possible beneficial effect of the adjunctive use of AZM on periodontal non-surgical treatment of ChP or AgP patients. For the therapy of both diseases, there are, however, no data available on the superiority of AZM against the standard antibiotic combination of metronidazole and amoxicillin. According to the limited external evidence available in this systematically performed analysis, AZM may therefore be very carefully regarded as a potential alternative antibiotic systemic drug in selected cases of ChP, particularly when contraindications for the standard protocol involving adjunctive amoxicillin and metronidazole are given.

Direction for further research

The consideration of the following parameters is suggested for future research:

1. Further evaluation of systemic AZM as an adjunct to SRP (in non-smokers and in patients with *smokers' periodontitis*)
2. Comparison of adjunctive systemic AZM to adjunctive amoxicillin and metronidazole in non-surgical SRP
3. Evaluation of the optimal SRP sequencing, when adjunctive systemic AZM is applied
4. Further investigation of the optimal starting point of the systemic AZM medication
5. Focus on clinically relevant outcome parameters such as on distinguished PD sites (moderate/deep)
6. Adequate sample size and observation times (≥6 months).

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Conflict of interest The authors declare that they have no conflict of interests.

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