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Management of Perioral Dermatitis in Adolescents and Adults

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1. SUMMARY

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Title: Management of Perioral Dermatitis in Adolescents and Adults

Aim: To review current scientific literature and to investigate management of perioral dermatitis in adolescents and adults.

Objectives:

1. To assess efficacy and safety of topical treatment options for perioral dermatitis
2. To assess efficacy and safety of systemic treatment options for perioral dermatitis
3. To prepare practical recommendations for perioral dermatitis treatment

Material and Methods: The collection of articles in this study were conducted with the PRISMA methodology. Keywords as 'Perioral dermatitis' Perioral dermatitis AND treatment', 'Perioral dermatitis AND management' were searched on the electronic database PubMed. An initial search revealed 595 articles in the PubMed database. Additional filters such as free full text, clinical trials, randomized controlled trials, articles published within 10 years, human species and articles in the English language were applied, which were then manually screened according to the eligibility criteria.

Results: A total of 6 studies were included to the study and in total, 382 study participants were included in this study to evaluate the effectiveness and safety of different topical and systemic treatment options.

Conclusions: Topical treatment with 3% praziquantel (PZO), 1% pimecrolimus, transient receptor potential vanilloid 1 (TRPV1) inhibitor 4-TBH, 1% erythromycin and oral tetracyclines effectively treated perioral dermatitis (POD), whilst 15% Azelaic acid (AzA) were concluded as ineffective. Conclusion regarding safety and efficacy of oral isotretinoin cannot be made due to lack of information. Oral tetracyclines are concluded to efficiently treat POD, but information of safety is missing to conclude the drug as safe.

Practical recommendations: Mild to moderate treatment of perioral dermatitis (POD) include a 5 weeklong zero therapy, followed by topical treatments if no improvement is seen. Further on if the patient is diagnosed with severe POD or if no improvement is noticed with topical therapies, systemic therapy is indicated. First line systemic therapy includes oral tetracyclines and later oral isotretinoin if clearance of lesions is not achieved. If triggering factor is considered to be a causative factor of POD, it should be eliminated if possible and other medical conditions allow.

2. ACKNOWLEDGMENTS

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3. CONFLICT OF INTEREST

The author reports no conflicts of interest.

4. BIOETHICS COMMITTEE APPROVAL

Approval from the Bioethics Committee was obtained to conduct the study (Nr. 2024-BEC2-163).

5. ABBREVIATION LIST

1. PZO: Praziquantel
2. TRPV1: Transient receptor potential vanilloid 1
3. POD: Perioral dermatitis
4. AzA: Azelaic acid
5. PAR2: protease activated receptor 2
6. IGA: Investigator’s global assessment scale
7. PODSI: Perioral dermatitis severity index
8. DLQI: Dermatology quality of life index
9. VAS: Visual analogue scale
10. NRS: Numeral rating scale
11. PRISMA: Preferred Reporting Items for the Systematic Reviews and Meta-Analysis
12. RCT: Randomized control trial
13. AEs: Adverse events
14. VEH: Vehicle group
15. PGA: Physician Global Assessment of Treatment
16. TFC: Total facial count

6. INTRODUCTION

POD is a common acneiform facial eruption, affecting mostly young and middle-aged women in the ages between 16 to 45 years old [1,2]. The exact prevalence of POD remains uncertain, but it had primarily been documented in 'Western Europe, Scandinavia, North America and Australia'[2]. Additionally, it has been linked to anxiety, depression, and suicidal thoughts [3,4]. Typical characteristics are grouped follicular papules and pustules on an erythematous skin base with variable scaling, leaving the lip margin unaffected [2,4]. In contrast to these characteristics, the sub-type of POD is the granulomatous form of POD, which shows granulomatous lesions when examined histologically [5,6].

There are different types of therapies for treating POD, which may be topical, or systemic. In addition to these two treatment options, zero therapy is another possible treatment option [7,8]. It consists of ceasing all topical therapies with special attention to topical steroids and lipid-rich cosmetics which may exacerbate the condition [7,8]. This therapy has the potential to enhance skin lesions in patients with POD without the need for medical intervention, with the requirement of good compliance by the patients [7,8]. Regardless, based on clinical experience, 'zero therapy is not well accepted by patients suffering from POD'[8]. This disapproval of zero therapy as a treatment option by the patients may lead to compliance issue [7,8].

With the current, yet limited reviews regarding the efficacy and safety on treating POD, this review aims to provide clinical and theoretical comprehension as to whether current data provides sufficient insights in the efficacy and safety of treating POD. In addition, it aims to accentuate areas where more studies are needed to achieve efficient and safe treatment of POD. Moreover, due to the link between POD and psychological diagnostics that may follow, as well as the dilemma regarding zero therapy, this review is advocated with the aim of highlighting the efficacy and safety of both topical and systemic treatment of POD.

7. AIM AND OBJECTIVES

AIM

To review current scientific literature and to investigate management of perioral dermatitis in adolescents and adults.

OBJECTIVES

1. To assess efficacy and safety of topical treatment options for perioral dermatitis
2. To assess efficacy and safety of systemic treatment options for perioral dermatitis
3. To prepare practical recommendations for perioral dermatitis treatment

8. LITERATURE REVIEW

8.1 Pathogenesis of perioral dermatitis

The exact pathogenesis of POD has yet to be established. However, certain factors have been considered to contribute to POD [9]. Among those, are glucocorticoids, various infective agents, hormonal as well as contact factors [2]. Women experiencing 'premenstrual deterioration' and the usage of hormonal prescription drugs may have been reported to cause POD [9,10]. In addition to these, contact agents such as fluorinated toothpaste, and face creams containing occlusive ingredients like petrolatum may also be factors contributing to POD [9,10]. However, neither of those factors correlates with POD diagnosis enough to be considered significant [9,10].

Moreover, cultures of lesions in diagnosed patients have revealed the growth of 'fusiform spirilla bacteria, Candida species, Demodex folliculorum, and other fungi'. Although, like in the aforementioned cases, is has not been considered relevant enough to be an established causative factor of POD [9]. According to Wilkinson et al. [10], extended usage of strong topical glucocorticoids is the only proven causative factor with significant correlation. POD is frequently seen in patients prescribed with potent glucocorticoids, which is typically applied locally, with 74% of these cases caused by Betnovate according to Cotterill et al. [11]. Moreover, POD has also been noticed in patients with prescribed glucocorticoid inhalations sprays nasally or through mouth [9]. Furthermore, observations have demonstrated that treatment with topical steroids may be beneficial at the beginning of POD treatment [9]. Although, when steroids are ceased, POD may reappear with worse lesions than prior to treatment with steroids [9].

8.2 Clinical forms of perioral dermatitis

In contrast to the previously described characteristics of POD, a variant called granulomatous POD may present with similar features of POD [12]. Misago et al. [12] highlights the difficulties regarding the etiology, diagnostics, and treatment of the granulomatous form of POD. According to the authors, there is currently a debate whether this form of POD should be a disorder by itself [12]. This is due to the findings when examining these lesions histologically, where granulomatous infiltrates are seen, which is caused by various topical or systemic agents [12,13]. Despite this, patients do not express systemic symptoms [13]. Due to this distinctive pattern, its arguable that this granulomatous form of POD has similarities to cutaneous sarcoidosis [12]. Whilst comparing these two forms of POD, the granulomatous form is commonly observed in pre-pubertal children affecting both sexes equally [13]. The lesions are more yellow to brown papulo-pustular in the similar regions of the face as POD [13].

8.3 Treatment options in perioral dermatitis

8.3.1 General information of treatment options in perioral dermatitis

Based on the current available literature, there appear to be no clear guidelines regarding treatment of patients with POD. This may cause challenges for the medical professionals when deciding the most safe and efficient treatment for their patients. A probable consequence of no clear guidelines might result in several topical and systemic options when treating POD without a clear understanding whether they are safe and efficient enough. Therefore, presentation of treatment options and their shown efficacy and safety may provide guidance needed for the medical professionals when deciding on treatment.

8.3.2 Zero therapy

Several treatment options have been proposed in the treatment of POD. One of the treatment options, which does not require medical intervention, is zero therapy, which as Lee and Zirwas [6] explained may be done in two ways. One of them aims to abruptly discontinue the steroids, which results in worsened lesions to a beginning, but a faster resolution [6]. By following this approach, resolution may be achieved within 1 to 3 months [6]. The other, slower approach aims to prescribe a less potent topical glucocorticoid and, as a result, cease the usage of steroids until fully discontinued [6]. By following this path when choosing zero therapy, patients will not experience flares to the same extent as when abruptly stopped [6]. However, it often takes patients greater than one year to fully reach resolution [6].

8.3.3 Medical interventions

Regarding treatment of POD with medical interventions, various drugs may be used. Treatments that have anti-inflammatory and anti-parasitic properties are frequently selected. Immunosuppressants such as topical calcineurin inhibitors have effectively been treating atopic dermatitis [14]. One calcineurin inhibitor, 1% pimecrolimus, has as well been used off-label to treat other dermatological lesions such as psoriasis and seborrheic dermatitis [14,15]. Further on, the bacteriostatic antibiotic macrolide, erythromycin, has been used in medicine for its similar properties to suppress inflammatory acne [16,17]. Erythromycin achieves this by preventing further growth of bacteria by inhibiting protein synthesis in the sebaceous follicle [16,17].

Other than the topical applied macrolide, ivermectin, which is frequently used in the treatment of rosacea, has shown to have both anti-inflammatory as well as anti-parasitic effects [18]. This action is mainly

performed by suppressing the production of inflammatory cytokines and tumor necrosis alpha [18]. Moreover, limited studies regarding the anthelmintic isoquinoline cestocide, praziquantel (PZO) have been performed [19]. However, PZO has shown to decrease the levels of the protein YKL-40, where increased serum levels of this protein have been seen in various inflammatory conditions such as psoriasis [19]. PZO is therefore thought to act as an anti-inflammatory agent in the treatment of POD [19]. Lastly, like the aforementioned drugs, AzA has similar anti-infective and anti-inflammatory effects when applied to the skin which is thought to have a healing effect on lesions [20].

One drug that is regularly prescribed within the dermatological field, is oral tetracyclines [21]. One of its mechanisms of action is inhibiting protease activated receptor 2 (PAR2), a receptor which plays a role in stimulating inflammatory interleukins [21]. Therefore, since oral tetracyclines inhibit this action, the end-result leads to an anti-inflammatory action [21]. In addition to this, studies evaluating the efficacy of treating POD, oral isotretinoin has been performed [22]. Isotretinoin has shown efficacy when treating acne, but the exact mechanism of action is not fully established [22].

8.5 Severity grading of perioral dermatitis

Prior to presenting the studies, one must be acquainted with how the majority of the studies define the severity of POD. The two main objective evaluations involve: investigator's global assessment scale (IGA) and perioral dermatitis severity index (PODSI) [6–8,18,19]. IGA is based on a 5-point scale ranging from 0-4, wherein 0 is classified as clear and 4 severe [18]. Rating 1 are those patients with minimal involvement, 2 points mild, and 3 is classified as moderate [18]. Regarding PODSI, erythema, papules and scaling is evaluated with a possible grading from 0 to 3 in each category, resulting in a PODSI score between 0-9 point [18]. Grade of 0.5-2.5 is classified as mild, 3.0-3.5 as moderate and 6.0-9.0 as severe [7]. Subjective evaluation can be performed by the patient in the form of dermatology quality of life index (DLQI) [6,7]. A questionnaire is provided to the patient to assess how the specific skin condition is affecting the patient from a scale of 0 to 30, where 0 equals no effect on the patient's life quality and 30 worse effects on life quality [7]. In addition, visual analogue scale (VAS) up to 10 points can be used to evaluate severity, itching, appearance as well as distension of the skin and subjective severity numeral rating score of 10 (NRS 10) [6,18].

9. RESEARCH METHODOLOGY AND METHODS

The study "Management of Perioral Dermatitis in Adolescents and Adults" was conducted by using Preferred Reporting Items for the Systematic Reviews and Meta-Analysis (PRISMA) method. The electronic database PubMed with keywords as 'Perioral dermatitis', 'Perioral dermatitis AND treatment', 'Perioral dermatitis AND management' were searched between June 19, 2023 and October 2, 2023. After the initial filters were applied, the studies were manually screened according to the inclusion and exclusion criteria listed in Table 1. Firstly, the abstracts were analysed and then the full articles were read to select the articles that were eligible for review. For every study selected to be reviewed, extraction data were the following: authors last name, year of publication, design of study, sample size, results, summary, and treatment strategies related to treatment of perioral dermatitis. (Figure 1).

Table 1: Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
Systemic reviews	Cohort studies
Randomized-control trials	Meta-analyzes
Non-randomized control trials	Literature reviews from other authors
Case reports	Editorials
Case series	Expert opinions
Research papers concentrated on adolescents and adults	Publication date more than 10 years
Articles in English	Articles only covering children
Free full text available	Articles not in English
Articles published within 10 years	Full articles not accessible
Publications relevant to research topic	
Gender of both men and women	

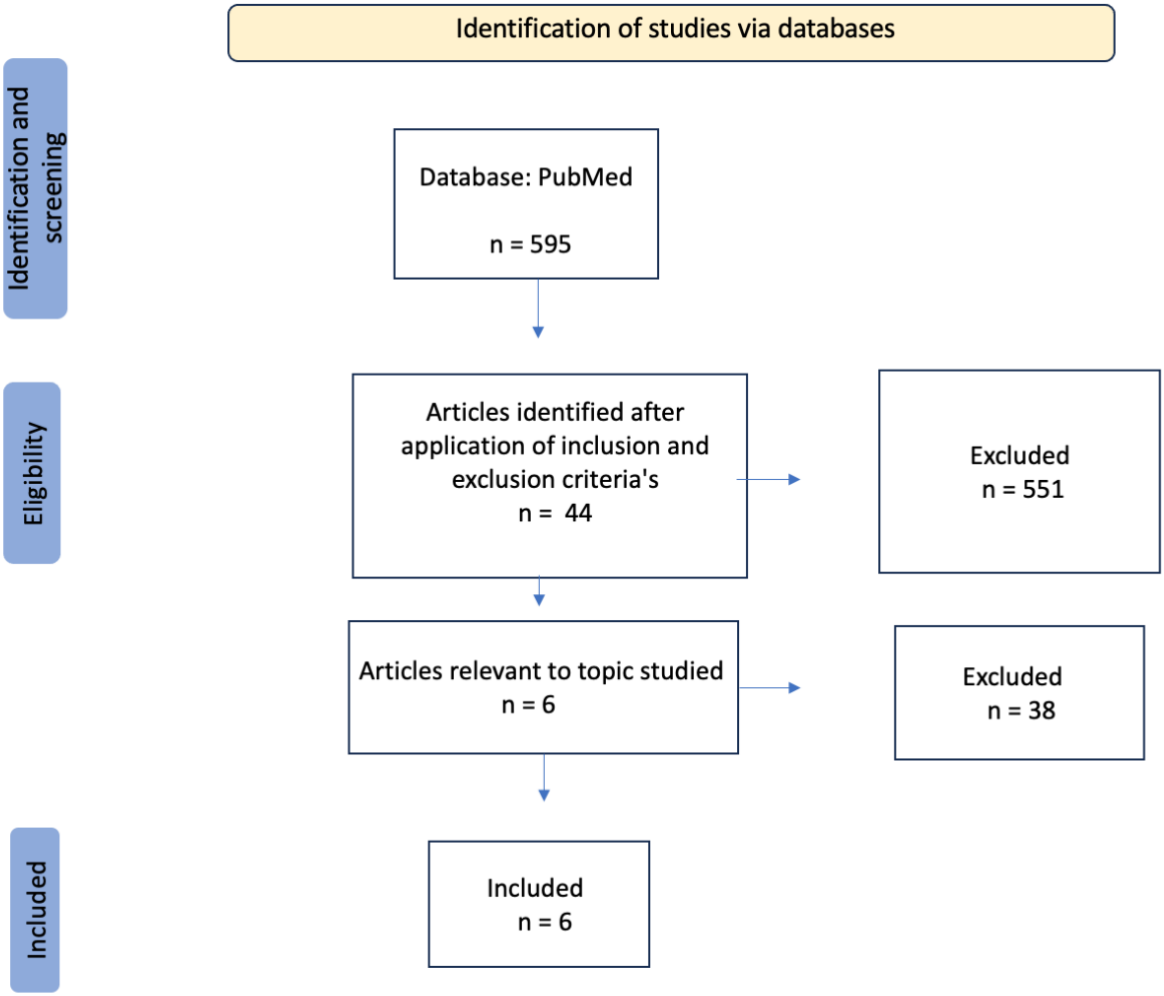


Figure 1: The literature search methodology

10. RESULTS AND THEIR DISCUSSION

10.1 General information of included studies

The studies in this review are classified into topical treatment with its efficacy and safety and systemic treatment respectively. The number of studies that are analyzed in this review according to the inclusion and exclusion consists of mostly studies evaluating topical treatment (n=5), compared to the systemic ones (n=1). In total, 382 participants were enrolled in this study evaluating the following study designs: Randomized control trials RCT (n=6), case series study (n=1), case study (n=2)

10.2 Efficacy of topical treatment in perioral dermatitis

In the included studies topical treatment was analyzed in 8 articles, with 6 different treatment agents. The different medical interventions presented and discussed in this section includes topical application of 3% PZO, 1% ivermectin, 1% pimecrolimus, TRPV1 inhibitor 4-TBH, 15% AzA as well as 1% erythromycin. Bribeche et al. [19] provided valuable insights from their single-centre, randomized, single-blind, vehicle-controlled pilot study with 46 participants. The study was conducted between November 2012 until August 2013, where the participants were instructed to apply the ointment twice daily for 4 weeks [19]. Evaluation of treatment was assessed during weeks 1,2,3,4 as well as week 8, where the patients had not applied the ointment from week 4 until week 8 [19]. Topical PZO 3% ointment decreased PODSI score ≥ 50% from baseline in 72.7% of the patients at week 4 compared to 52.3% in the placebo group ($P<0.001$) [19]. Moreover, at week 4, an IGA rating of clear or minimal was achieved in a significantly greater proportion of patients in the PZQ group (82%) compared with the placebo group (43%) ($P < 0.001$) [19]. However, whilst measuring PODSI at week 8, no statistical significance was obtained compared to placebo group [19]. There could be different reasons to this, one may be that 3% PZO given topically is more efficient during the first 4 weeks and after it might decrease in efficiency. Although, while comparing whether an active ingredient, 3% PZO in this case is efficient, it should be weighed against a placebo. In case of POD, a placebo cream could be corresponding to a so-called zero therapy, which is also a recognized treatment of POD. Therefore, it may be challenging comparing the two groups in the later stages of treatment since the skin lesions might heal due to the placebo cream taking the action as zero therapy. However, regarding the subjective DLQI both groups experienced an improvement in DLQI, but a quicker and more significant improvement was noted in the group treated with 3% PZO which might add to the probability of 3% PZO being efficiently treats patients with POD. Although it should be noted that this is as well a subjective evaluation done by the patient which is based on experience of the patient rather than a fact. On the other hand, by deciding to measure this variable which illustrates an important role in the quality of life of the

patient, the subjectivity of DLQI might not play a substantial role in deciding whether the results shown are trustworthy enough since satisfaction of the patient is the main end goal.

Barańska-Rybak et al. [18] Investigated whether application of 1% ivermectin once daily may improve mild to moderate POD. The number of participants diagnosed with POD were 8, where four patients with POD achieved IGA 0–1 after 4 weeks of treatment, 1 patient after 5 weeks, 2 patients after 6 weeks and 1 patient after 12 weeks [18]. Furthermore, Charnowski et. al [23] conducted a case study of an 18-year-old man with symptoms of POD. The man was previously treated with glucocorticoid steroids and 1% pimecrolimus without any significant improvement [23]. Results reported that the young man had improvements of skin lesions from week 4 onwards [23]. In neither of the studies flares were noticed during the 8 weeklong follow up period in the case study as well as in the 18 weeklong follow up containing the 8 participants [18,23]. Even though both studies accentuate the importance of further studies due to the small sample sizes in both studies in order to confirm these results, one cannot stress this enough. The total number of 9 participants in two studies is a rather small sample size and by increasing the number of participants and the duration of study, one may speculate that there will be greater segregation of results regarding efficacy of treatment as well as recurrence of POD. More accurate results regarding the efficacy and safety of applying ivermectin would be retained by increasing the sample size, the duration of the studies with its follow up as well as the possibility for the patients to fill in the recognized DLQI questionnaire in order to more accurately evaluate the subjective improvement of the patients. In addition, studies conducted in a randomized, double-blinded manner would further contribute to more trustworthy evidence regarding the efficacy and safety of ivermectin.

Schwarz et al. [24] and Oppel et al. [25] evaluated if 1% pimecrolimus cream applied twice daily was able to improve POD. Both studies were randomized and double-blinded where the groups of participants were randomly assessed into 2 groups, one receiving placebo cream and the other 1% pimecrolimus cream [24,25]. In the study conducted by Schwarz et al. [24], a total of 124 participants were included to apply the ointment for a total of 4 weeks or until lesions were cleared. Later on, this was followed up by 8 weeks of treatment free period to evaluate possible flares [24]. From the group treated with the active pimecrolimus ointment, 63% of the enrolled patients were classified as score 3 on the IGA scale [24]. Similarly to this, 54% of the patients in the vehicle group had received the same grade on the IGA scale [24]. Oppel et al. [25] enrolled in total 40 participants, with 20 participants in each group. In total the study took place throughout 8 weeks, where 4 of them the patients applied the creams and 4 that were aimed for a follow up [25]. The participants with a moderate or severe diagnosed POD were eligible for the study [25]. The mean PODSI score from pimecrolimus group was 4.5 in the beginning of the study and 4.6 in the vehicle group [25].

Oppel et al. [25] reports treatment of POD with 1% pimecrolimus demonstrated clinical significance during the first week but not during week 2. Corresponding results were demonstrated in the study by Schwarz et al. [24], where 40% of patients treated with pimecrolimus had a decrease in the PODSI score with 50% or more compared with 10% in the vehicle group. However, the difference between the two groups were reduced throughout the study, comparing 65% versus 59.4% in the vehicle group between the groups on day 29 [24]. As presented before, it might be challenging comparing the placebo to an active ingredient due to the placebo acting as a null therapy. Due to the smaller difference between the percentages on day 29 of the study, one may correlate it to that the participants in the vehicle group are improving due to the zero therapy done by applying a placebo cream. On the grounds of no statistical significance between receiving pimecrolimus compared to placebo after 1 week, these studies suggest that 1% pimecrolimus may be more beneficial during a time span up to 8 days regarding the measurement presented regarding PODSI. However, one must be aware that such short treatment period may induce a flare than if treated for a longer period. The subjective measurements VAS 10 as well as DLQI had a greater improvement in both studies. Oppel et al. [25] showing statistical significance of P=0.008 after 2 weeks and mean DLQI value of 3.3 compared to 4.2 at 29th day in the other study conducted by Schwarz et al. [24].

Another topical treatment option was assessed by Srour et al. [8] investigating the transient receptor potential vanilloid 1 (TRPV1) inhibitor 4-t-butylcyclohexanol cream [8,26]. This was an open, non-blinded trial containing in total 48 patients [8]. The ingredient was tested in a skin cream Eucerin UltraSENSITIVE®, which was sponsored by Eucerin [8]. The participants enrolled were instructed to apply the face cream twice daily for 8 weeks, with follow up occurring at week 4 and at the end of week 8 [8]. Mean PODSI at the beginning of the study was 4.71 ± 1.37, which decreased to 2.83 ± 1.75 at week 4 and showed continuous improvement until the last evaluation at week 8 ($P<0.0001$) [8]. Regarding the subjective measurements, the study provided results showing significant improvement whilst measuring NRS 10, which was reduced from 6.74 ± 1.93 to 4.51 ± 2.61 after 4 weeks [8]. In addition to NRS 10, DLQI was decreased from 10.07 ± 5.21 at baseline to 2.19 ± 2.94 at week 8 ($P<0.0001$) [8]. Although, these results should be investigated further in order to confirm the results shown in this study. Preferably, a study without a sponsor to decrease the probability of biased results, or with a possibility to perform the trial in a double-blinded manner as well as increased sample size.

In addition to the studies presented, topical application of 15% AzA was applied twice daily throughout a 6 weeklong, randomized, and double-blinded study [27]. The study participants (n=46) were divided into two groups (30 treated with AzA and 16 with placebo) [27]. Improvements were assessed during 4 visits (baseline, week 2, 4 and 6) where IGA and adverse events were assessed [27]. The results of the study showed no significant improvement in patients treated with 15% AzA compared to the vehicle group (62.1% versus 62.5% for the

vehicle group) after 6 weeks of treatment [27]. During December 1981 and March 1983, topical erythromycin 1% was one of the active ingredients evaluated in 33 patients [28]. However, with frequency not stated [28]. In the same study, oral tetracyclines (n=35) were also assessed as well as a vehicle group receiving a placebo pill (n=31) [28]. Patients were invited every 10th day for evaluation of papules [28]. Topical erythromycin appeared to not have a significant result on day 10, compared to oral tetracyclines and placebo [28]. From day 20, erythromycin and tetracycline had improved, by decreasing the number of papules ($P<0.001$) [28]. Topical erythromycin were superior regarding the number of papules compared to placebo on days 20 until day 60, with no significant difference on day 70 and 80. This may indicate that applying topical erythromycin is only beneficial up to 60 days until zero therapy is equal to medical intervention of topical erythromycin.

10.3 Safety of topical treatment options in perioral dermatitis

Regarding safety, with the application of 3% PZO ointment as well as ivermectin, patients reported adverse effects such as dryness of mild intensity as well as burning and tingling [18,19,23]. After applying moisturizer, the feeling of dryness disappeared, and it did not result in treatment discontinuation [18,19,24]. Application of a skin care cream with the ingredient TRPV1 inhibitor 4-t-butylcyclohexanol resulted in one third, i.e. 16 participants complaining of erythema and tenderness of the skin [8]. This reaction occurred in the first week of trial and the authors considered the reaction as mild [8]. The application of topical calcineurin and topical erythromycin may result in adverse effects such as erythema, burning sensation and pruritus with 91% classified as mild [24,25,28].

Schwarz et al. [24] reported that out of the 79 participants who completed the follow up period, 10 patients from the 1% pimecrolimus group had a relapse of POD, compared to 6 from the vehicle group. From the studies presented about the efficacy and safety of 1% pimecrolimus cream applied topically, an extended follow up period would be favorable in order to evaluate the extent of flares experienced by the patients treated with pimecrolimus. In addition to this, by using calcineurin inhibitors one may be more susceptible to developing herpes simplex infections [24]. The author reported that one participant withdrew treatment with AzA due to adverse events, however, the author did not specify what adverse event [27]. Moreover, common side effects noted by participants were irritation and itchiness confined to the face [27].

It may be challenging to classify the severity of adverse effects that can accompany topical treatment for POD. The studies presented in this section all present side effects that are mostly considered as mild, with examples of erythema, burning as well as feeling of dryness. One must be aware that patients might evaluate their

side effects differently. Therefore, evaluation should be individualized to the patients and their experience rather than just the objective findings.

10.4 Efficacy of systemic treatment options in perioral dermatitis

This section will cover 2 studies, one case study of a woman in her thirties diagnosed with granulomatous variant of POD treated with oral isotretinoin as well as topical metronidazole. In the other study, oral tetracyclines will be evaluated which were evaluated in the same study as topical erythromycin presented previously.

In the case study, 20 mg of isotretinoin was given orally together with topical metronidazole [29]. The woman was previously treated with both steroids, which resulted in worse lesions and as well as doxycycline that showed no improvement [29]. Five days into the treatment with isotretinoin and metronidazole, the patient experienced worsening of lesions but was advised to continue her treatment [29]. After 3 weeks of isotretinoin, the skin lesions had improved [29]. No values such as PODSI, IGA, DLQI or VAS 10 were measured which complicates the reasoning whether treatment was effective. In addition to this, since the patient was co-treated with topical metronidazole, one cannot fully correlate the improvement of lesions to the treatment with isotretinoin only. Furthermore, the study did not mention whether side effects were present, where serious side effects are rare but possible. This is an important factor since treatment efficacy ideally should be evaluated with a benefit and risk assessment.

Lastly, one study by Weber et al. [28] presented, as previously described topical erythromycin, oral tetracyclines and placebo pill. The systemic therapy from the study, which involved prescribing 500 mg of tetracyclines for 10 days, followed by 250 mg for a further 10 days, will be discussed in this section. This treatment option was also assessed every 10th day and evaluated positive if the number of papules were decreased [28]. Results of the study showed that tetracycline improved the papules compared to placebo ($P<0.001$) starting from the 20th day [28]. Less significant improvements were noted when comparing the tetracyclines with topical erythromycin showing a P-value of 0.052 [28]. Comparing the tetracyclines with the placebo group, the 35 participants treated with tetracyclines had fewer papules on days 20,30,40 and 50 [28]. Similarly to topical erythromycin, no significant improvement was noticed between the placebo and oral tetracyclines after day 50 onwards [28]. Since there was no significant difference between the oral tetracyclines and topical erythromycin, evaluation of whether receiving oral antibiotics are superior to a more local treatment is necessary. Additionally, regarding systemic treatment for POD, qualitative and quantitative information from the last 10 years is lacking. Reasons may be various, ranging from increased demand of topical treatment leading to decreased interest in

systemic treatment. Another idea might be lack of proven efficacy in combination with risk of systemic side effects that may accompany oral treatment. As important variables regarding the efficacy of isotretinoin given with metronidazole as a systemic treatment were not acknowledged in the above-mentioned case report, further studies are required to evaluate its efficacy. In addition to this, more updates studies are required to acknowledge the efficacy and safety of oral tetracyclines as a systemic treatment, as the study used was performed roughly 40 years ago.

10.5 Safety of systemic treatment options in perioral dermatitis

Regarding safety of oral tetracyclines, the study conducted by Weber et al. [28] presented adverse events such as abdominal discomfort, facial dryness, and pruritus. However, it was not mentioned whether the participants discontinued the treatment because of the adverse events [28]. Isotretinoin is commonly used for treatment for acne vulgaris, and common adverse events are dose dependent [30]. As previously discussed, the study did not mention if there were any side effects noticed, expect for the worsening of lesions [29]. Other adverse events that may accompany the usage of oral isotretinoin are increasement of liver enzymes, such as LDL-cholesterol, triglycerides, and transaminases, although these adverse events are uncommon and reversible [30]. Depression and inflammatory bowel disease are classified as severe adverse events, yet they are rare, and author mentions that it should not condone using the preparate [30]. It’s necessary that future studies specify when oral treatment should be given to patients. Adverse effects of oral tetracyclines compared to other topical treatments presented in addition to facial dryness, and pruritus with abdominal discomfort. Future studies regarding safety of oral treatment with tetracyclines should further assess the risks and benefit to treat patients more efficiently with minimal side effects as possible.

Table 2: Summary of studies

Study and year	Study design	Parameters	Duration	Intervention	No. Of participants	Effect at the end of intervention	Most efficient effect during intervention	Side effects
Author: Bribeche et al. [19] *Period:* November 2012 to August 2013	RCT, single-blinded	PODSI, IGA and DLQI, AEs	8 weeks	3% praziquantel ointment	Total study population (n=46) 3% PZO ointment group (n=23) Vehicle (VEH) group (n=23)	Week 4 PODSI (P<0.001) IGA (P<0.001) DLQI (P<0.001)	- - -	Mild dryness
Author: Barańska-Rybak et al. [18] *Period:* November 2016 to July 2017	Case series study	IGA, Physician Global Assessment of Treatment (PGA) and AEs	1 to 3 months depending on response	1% Ivermectin	Total study population with POD (n= 8)	IGA "clear"/ "almost clear" by week 12 for all 8 patients	50% of patients scored "clear"/" almost clear at week 4	Dryness, burning, tingling sensation
Author: Charnowski et al. [23] *Period:* -	Case study	-	12 weeks	1% Ivermectin	Total study population (n=1)	At week 12, no rash were noticed	Improvement from week 4	-
Author: Oppel et al. [25] *Period:* -	RCT, double-blinded, single-centered	PODSI, DLQI, AEs	8 weeks	1% pimecrolimus	Total study population (n=40) 1% pimecrolimus group (n=20) VEH (n=20)	Week 4 PODSI (P = 0.02) POD score regarding scaling (P=0.14) DLQI (P= 0.26)	PODSI most efficient (P = 0.005) day 7 POD score regarding scaling most efficient (P = 0.002) day 7 DLQI (P = 0.008) day 14	Heat sensation, erythema, worsening of skin, pruritus and herpes labialis
Author: Schwarz et al. [24] *Period:* -	RCT, double-blinded, multicenter	PODSI decrease by 50% from baseline, IGA, VAS, DLQI, AEs	12 weeks	1% pimecrolimus	Total study population (n= 124) Pimecrolimus group (n=60) VEH (n=64)	Week 4 PODSI decrease by 50% from baseline (P= 0.5191) IGA (10% in pimecrolimus group with complete remission, 7.8% in the vehicle group) VAS average over the 4 weeks (P = 0.0250) DLQI average over the 4 weeks (P = 0.0071)	PODSI decrease by 50% from baseline most efficient day 15 (P = 0.0015) IGA day 8 (15% in pimecrolimus group with complete remission or classified as almost clear, 1.6% in the vehicle group) -	Herpes simplex, burning sensation, erythema and pruritus

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Author: Srour et al. [8] *Period*: 2020	Non-blinded clinical trial	PODSI, DLQI and NRS 10, AEs	8 weeks	TRPV1 inhibitor 4-TBH	Total study population n=48 (42 women, 6 men)	PODSI (P<0.0001) NRS 10 (P<0.0001) DLQI (P<0.0001)	All P-values remained the same	Erythema and skin tenderness
Author: Bayer HealthCare et al. [27] *Period:* November 2006 to March 2007	Double-blinded, vehicle-controlled, RCT, multi-centered pilot study	POD sum score, Total facial count (TFC), IGA and patient's assessment on overall improvement, AEs	6 weeks	Azelaic acid 15% (AzA)	Total population (n=46) AzA group (n=30) VEH (n=16)	POD sum score from baseline (median) Aza (-7) VEH (-8) IGA reaching significant results at last visit AzA (73.3%) VEH (68.8%) Patient's assessment on overall improvement Aza (51.7%) VEH (50.0%)	- - -	Site irritation of application
Author: Weber et al. [28] *Period:* December 1981 to March 1983	RCT, prospective, placebo-controlled therapeutic study	Papule count, AEs	80 days	1% topical erythromycin	Total study population of topical erythromycin (n=33)	Measurements at days 70 and 80 No significant difference on papule count compared to placebo	Papule count compared to placebo on days 20 to day 60 (P = 0.004, 0.04, 0.07, 0.03 and 0.02)	Burning sensation
Author: Tambe et al. [29] *Period:* -	Case study	-	-	20 mg Isotretinoin / day	Total study population (n=1)	No end of treatment is mentioned	Improvement of skin lesions at week 3	Exacerbation of skin lesions
Author: Weber et al. [28] *Period:* December 1981 to March 1983	RCT, prospective, placebo-controlled therapeutic study	Papule count, AEs	80 days	500 mg tetracycline x2/day, later 250 mg x2/day	Total study population of oral tetracyclines (n=35)	Measurements at days 70 and 80 No significant difference on papule count compared to placebo	Papule count compared to placebo on days 20 to day 50 (P= 0.0001, 0.001, 0.001 and 0.2)	Burning sensation, abdominal distress

IGA: Investigator's global assessment scale, PODSI: Perioral dermatitis severity index, DLQI: Dermatology quality of life index, VAS: Visual analogue scale, NRS: Numeral rating scale, RCT: Randomized control trial, PZO: Praziquantel, AEs: Adverse events, VEH: Vehicle group, PGA: Physician Global Assessment of Treatment, TFC: Total facial count

11. CONCLUSION

1. Topical treatment with 3% PZO, 1% pimecrolimus, TRPV1 inhibitor 4-TBH and 1% erythromycin were shown effective, although 15% AzA were shown to not treat POD effectively. The treatment options concluded to be efficient, are also concluded to be safe in the treatment of POD, including 15% AzA. Regarding 1% ivermectin, a clear conclusion regarding efficacy and safety cannot be made. This is due to the special note of performing further research about its efficacy and safety with a larger sample size.

2. Isotretinoin (20mg) cannot be established as both safe and efficient due to lacking information defining efficacy and safety. Moreover, oral tetracyclines are efficient when treating POD, due to not enough information regarding withdrawal from medicine due to side effects are missing, more information is needed to be provided before concluding that oral tetracyclines are safe.

3. After diagnosis of POD is made, and if a triggering factor is known, it should be eliminated if possible and if other medical conditions allow. For mild to moderate POD, zero therapy is recommended for a duration of 5 weeks. In case of no improvement is noticed, treatment with topical medical interventions is preferred. If severe POD is diagnosed, or no result of improvement of topical therapies in case of mild to moderate POD, systemic treatment is recommended. First line treatment of systemic options are oral tetracyclines. If no clearance of lesions is achieved after fulfilled treatment, oral isotretinoin is the last drug recommended.

12. PRACTICAL RECOMMENDATIONS

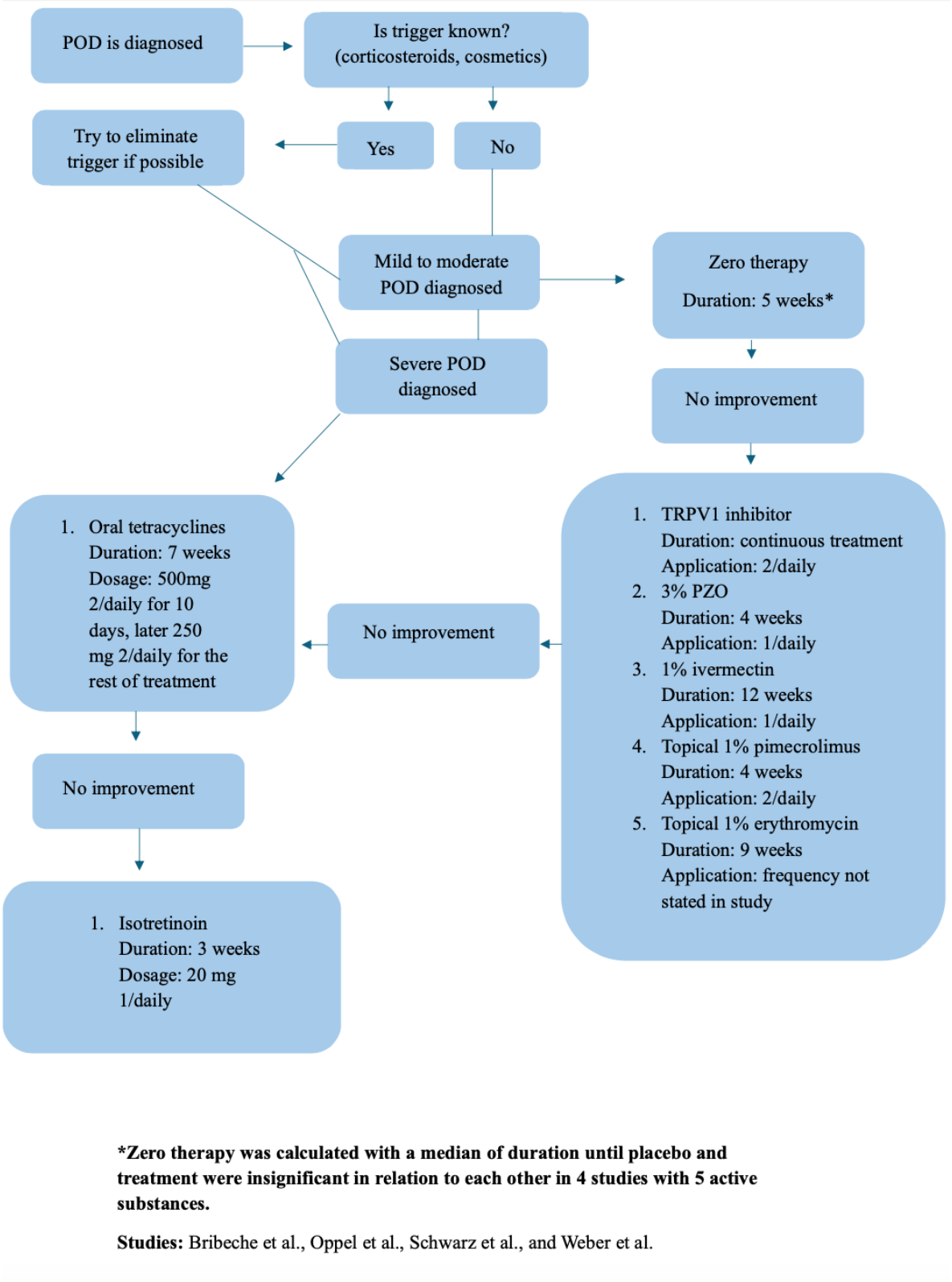


Figure 2. Practical recommendations

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