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Review Article

Risk of Relapse Upon Treatment Discontinuation in Rosacea: An Updated Systematic Review and Network Meta-Analysis of Randomized Controlled Trials

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Background: Rosacea treatments often lead to recurrence after discontinuation, highlighting the need for effective maintenance therapies. The long-term efficacy of treatments in preventing relapse has not been systematically compared.
Objectives: To compare the risk of relapse upon treatment discontinuation after achieving clinical remission with both topical and systemic therapies.
Methods: Updated systematic review and network meta-analysis of randomized controlled studies following PRISMA guidelines. A thorough literature search across different databases to identify randomized controlled trials (RCTs) on treatment relapse rates in adult patients with moderate to severe papulopustular rosacea treated with systemic and topical treatments was conducted. Data were independently extracted, and the risk of bias was assessed using the Cochrane tool. Statistical analyses were performed using network meta-analysis with random effects models.
Results: A total of seven out of an initial 14,450 articles screened were retrieved, involving 632 patients with moderate to severe rosacea and 552 controls treated with metronidazole 0.75% gel, doxycycline 40 mg, ivermectin 1% cream, isotretinoin 0.25 mg/kg/day, hydroxychloroquine 200 mg, and aminolevulinic acid photodynamic therapy. Results showed that isotretinoin and metronidazole significantly prevented rosacea relapse compared to placebo, with isotretinoin ranked as the most effective treatment according to SUCRA rankings. The average time regarding relapse varied among studies, with metronidazole showing a shorter relapse period (12 weeks) than ivermectin (21 weeks). The risk of bias was low, with no significant publication bias detected. The limits of this review were the relatively small number of studies included and the high degree of indirectness that was noted across these studies, potentially affecting the reliability of some estimates.
Conclusion: Rosacea remission can be maintained for a certain period of time after the discontinuation of the treatment and also during the treatments. Isotretinoin might be effective in reducing the risk of relapse.

Keywords: network meta-analysis; relapse; rosacea; systematic review

1. Introduction

Rosacea is a chronic, inflammatory skin disease that affects the central region of the face characterized by erythema, papules, pustules, telangiectasia, and recurrent flushing [1]. For inflammatory lesions, first-line treatments include topical ivermectin, azelaic acid, and metronidazole. For moderate-to-severe inflammatory lesions and inflamed phymas, modified-release oral doxycycline of 40 mg, oral tetracycline, and low-dose oral isotretinoin are

recommended. Even if these treatments are effective, once they are discontinued, there is a risk of recurrence after a variable period. Therefore, maintenance therapy is recommended, preferably with the use of a topical treatment. Although there are some meta-analyses comparing the efficacy of various treatments [2], the impact of these treatments on maintaining a prolonged disease-free period in rosacea has not been systematically compared.

We undertook an updated systematic review and network meta-analysis (NMA) of randomized controlled studies to compare the risk of relapse upon treatment discontinuation once clinical remission has been achieved following topical and systemic treatments.

2. Methods

2.1. Registration of the Protocol. The protocol of this systematic review and meta-analysis was registered in PROSPERO (CRD42024565456, June 25, 2024).

We performed the systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the NMA statements [3]. We conducted a systematic literature search from the inception date to June 25, 2024, in MEDLINE via PubMed and Ovid, Embase, Scopus, Web of Science, ClinicalTrials.gov, and Cochrane Library to identify randomized controlled trial (RCT) studies examining the risk of relapse of rosacea among individuals who were treated with systemic and topical treatments. No other additional sources were consulted. References of relevant original papers and review articles were also screened for other eligible studies potentially not covered by the original database search.

Search text terms were as follows: ((“treatment” [Mesh] OR “therapy” [Mesh] OR “randomized” [Mesh] OR “controlled” [Mesh] OR “trial” [Mesh]) AND (“rosacea” [Mesh]). There were no restrictions in terms of gender, race, language, or geographic area.

2.2. Study Selection. We followed the population–intervention–comparison–outcomes–study design (PICOS) model for defining our eligibility criteria [4]. Population included adult patients with a clinically diagnosed papulopustular rosacea classified from moderate to severe before treatment achieving clinical remission as defined by an investigator global assessment (IGA) score of “clear” or “near clear” (IGA 0, 1) [5]. Interventions included any systemic or topical treatment delivered as monotherapy or in combination. Comparisons included either placebo or active comparators. The outcomes of interest were the proportion of relapse, defined as the proportion of patients with an increase in inflammatory lesion count by ≥ 50% of the lesion count reduction observed at Week 16 or patients with return to the baseline lesion count or to the baseline IGA, or any clinical condition which, in the judgment of the investigator, warranted a change in rosacea treatment. Only randomized, controlled trials were included. Criteria for exclusion of the studies from the meta-analysis were as follows: conference abstracts, case reports, theses, reviews, commentaries, editorials, practice guidelines, observational studies, case–control studies, and studies conducted in the pediatric population (< 18 years).

2.3. Data Extraction. Data from studies eligible for the aggregate data meta-analysis were independently extracted by two authors (I.T. and I.S.). Any disagreements were resolved by consensus and a third author if needed (A.P.). For all eligible studies, we extracted information on publication year, study design, study country, sample size, population characteristics, rosacea severity assessed by IGA score, rosacea response of treatments (IGA 0 or 1), time for relapse, and the proportion of patients having a relapse of rosacea. In case of duplicate publications, we included the most up-to-date or comprehensive information. The extracted data were collected and managed on a Microsoft Excel spreadsheet. No author was contacted in case of missing data.

2.4. Outcome Measures. For dichotomous outcomes, such as the proportion of patients having a rosacea relapse, we compared the number of participants with this occurrence against the total number of participants in the primary study who achieved clinical remission. Then, we calculated odds ratios (ORs) with their 95% confidence intervals (CIs) as the effect measure.

2.5. Risk of Bias. Two authors (I.T. and I.S.) independently assessed the risk of bias using the Cochrane Risk of Bias tool (RoB 2) [6]. The following items were analyzed: bias arising from the randomization process, bias due to deviations from the intended interventions, bias in the measurement of outcomes, bias in the handling of missing data, and bias in the selection of the reported result. Each domain was evaluated and classified as “low risk,” “high risk,” or “some concerns” regarding bias. Any discrepancies were addressed by a revaluation of the original article by the third author (F.B.).

2.6. Assessment of Heterogeneity. Statistical heterogeneity for pairwise comparisons was not assessed using the I^2 statistic because there were no pairwise comparisons [7]. For the NMA, we assumed a common estimate for the heterogeneity variance across different comparisons based on the heterogeneity variance parameter (Tau^2) estimated from the NMA models. Publication bias was evaluated using the funnel plot inspection.

2.7. Assessment of Statistical Inconsistency. To evaluate local inconsistency, we used the node splitting approach, which examines the agreement between direct and indirect evidence for each treatment comparison [8]. To evaluate the assumption of consistency across the entire network, we employed the “design by treatment” interaction model, accounting for various sources of inconsistency, such as differences in study designs and inconsistencies between direct and indirect evidence [9]. The Wald test was used for global consistency.

2.8. NMA Method. We performed all quantitative analyses on an intention-to-treat basis to preserve randomization within studies [10]. We applied the DerSimonian and Laird random effects model for the NMA. All statistical tests were two-sided and used a significance level of $p < 0.05$. We used Review Manager Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and the NMA package in STATA software v18 (StataCorp, College Station, Texas, USA) for all statistical analyses.

3. Results

3.1. Characteristics of the Included Articles. The PRISMA study flowchart describing the screening procedure of the articles included in the study is reported in Figure 1. From a total of 14,450 retrieved articles, 3626 found on PubMed-Embase, 8119 on Scopus, and 2705 on Web of Science, after excluding 486 duplicates, a total of 306 studies were identified based on title and abstract. After full-text examination of these 306 potentially eligible studies, we excluded 299 studies because of dissatisfactory inclusion criteria or unacceptable outcome measures. After this exclusion, a total of 7 RCTs were analyzed in this meta-analysis [11–17]. In particular, the main characteristics of the 7 eligible studies are reported in Table 1.

Overall, these RCT studies had aggregate data on 632 moderate/severe papulopustular rosacea patients who responded to systemic or topical treatments (IGA 0 or 1) and 552 controls. Demographic characteristics of the included patients are summarized in Supporting Table 1.

Three studies were carried out in Europe (France and the Netherlands) [12–14], 2 studies in Asia (China) [15, 17], and 2 studies in the United States [11, 16]. The treatments used in these studies included metronidazole 0.75% gel, doxycycline 40 mg, ivermectin 1% cream, isotretinoin 0.25 mg/kg/day, hydroxychloroquine 200 mg, and aminolevulinic acid photodynamic therapy (ALA-PDT). In this last study, patients underwent 3 to 5 sessions of ALA-PDT treatment every 1 or 2 weeks [17]. Lesions were irradiated with 633–610-nm light-emitting diode red light (Kernel Medical Equipment Co Ltd) at a power density of 30 mW/cm^2 for 1 h [17].

Three studies had placebo as comparator group, namely, isotretinoin 0.25 mg/kg/day vs. placebo [14], doxycycline 40 mg vs. placebo [16], and metronidazole 0.75% vs. placebo [11]. The others compared hydroxychloroquine 200 mg vs. doxycycline 100 mg [15], ALA-PDT vs. minocycline 100 mg [17], ivermectin 1% vs. metronidazole 0.75% [13], and doxycycline 40 mg vs. minocycline 100 mg [12]. The network plot summarizing the different treatment arms is shown in Figure 2. The follow-up period of observation ranged from 12 to 40 weeks, in particular, 12 weeks in two studies, 16 weeks in two studies, 24 weeks in two studies, and up to 40 weeks in one single study.

3.2. Risk of Relapse. The results of the pairwise comparisons are summarized in the forest plot (Figure 3). Both systemic and topical treatments were shown to prevent rosacea recurrence compared to placebo. In particular, from direct comparisons, both isotretinoin and metronidazole treatment resulted in a significant prevention of recurrence versus placebo. When considering indirect comparisons, ivermectin, minocycline, and ALA-PDT were shown to be effective. Conversely, doxycycline and hydroxychloroquine were found to be not superior to placebo. Further comparisons are summarized in the league table (Table 2). The results of the SUCRA rankings are shown in Supporting Figure 1. SUCRA ranking provides a summary of the relative effectiveness of each treatment. The SUCRA value ranges from 0 to 1, where a higher value indicates a higher probability of the treatment being among the best options to prevent rosacea relapse. According to the SUCRA rankings, isotretinoin had the highest ranking with a SUCRA value of 1, suggesting it is the most effective treatment among those compared. ALA-PDT and minocycline followed closely with a SUCRA value of 0.9 and 0.7, respectively, indicating that they are also highly effective options. Ivermectin, metronidazole, and doxycycline had a lower SUCRA value of 0.5, 0.3, and 0.3, respectively.

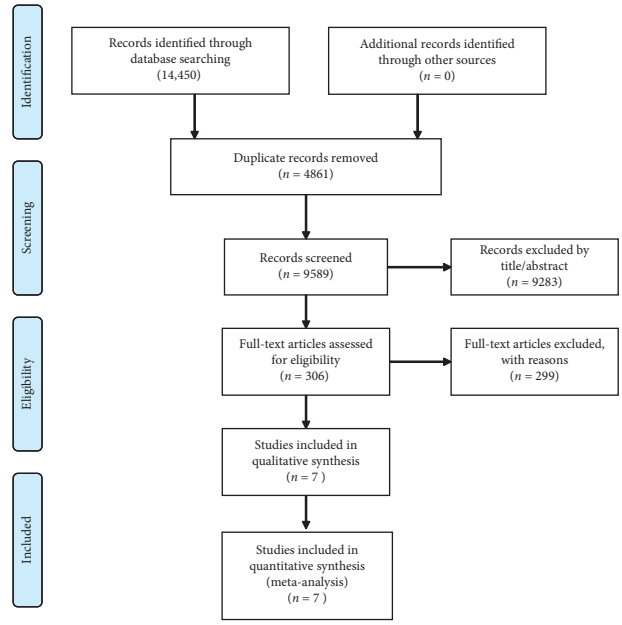

Figure 1: PRISMA study flowchart.

3.3. Average and Median Time to Relapse. Three studies evaluated the average time of relapse [11, 13, 17] and one study evaluated the median time of relapse [13]. In particular, Dahl et al. [11] reported a mean time of relapse of 12 weeks for patients treated with metronidazole 0.75% gel. Yang et al. [17] reported an average time of relapse of 24 weeks for patients treated with minocycline 100 mg and ALA-PDT. Taieb et al. [13] reported an average time of relapse of 21 ± 1 weeks for patients treated with ivermectin 1% vs. 19 ± 1 weeks for those treated with metronidazole 0.75% cream. The median time of relapse was only reported for Taieb et al. [13], resulting in 16 weeks (range 16–23) for patients treated with ivermectin 1% cream and 12 weeks

Table 1: Characteristics of the included studies.

References (doi)	Country/ region	Drugs	Controls	Duration of follow-up (weeks)	Patients	Patients who relapsed (%)	Controls	Controls who relapsed (%)	Age, years	Average time of relapse of patients (weeks)	Median time of relapse of patients (weeks)
Dahl et al., 1998 [11]	United States	Metronidazole 0.75% gel	Placebo	24	44	9/44 (20.45)	44	18/44 (40.9)	46.15	12	
van der Linden et al., 2016 [12]	Europe	Doxycycline 40 mg	Minocycline 100 mg	12	25	12/25 (48)	30	2/30 (6.7)	46		
Taieb et al., 2016 [13]	Europe	Ivermectin 1% cream (IVM)	Metronidazole 0.75% cream (MET)	16	399	250/399 (62.7)	358	245/358 (68.4)	52	21 ± 0.66 (IVM) 19.08 ± 0.73 (MET)	16.4 (16.14–23.57) (IVM) 12.14 (12.14–16.14) (MET)
Sbidian et al., 2016 [14]	Europe	Isotretinoin 0.25 mg/kg/ day	Placebo	16	51	0/51 (52.90)	5	5/5 (100)	47.5		15
Wang et al., 2021 [15]	China	Hydroxychloroquine 200 mg	Doxycycline 100 mg	12	28	4/28 (14.3)	30	3/30 (10)	33.7		
Del Rosso et al., 2022 [16]	United States	Doxycycline 40 mg	Placebo	40	65	9/65 (13.8)	65	18/65 (27.7)	47.2		
Yang et al., 2023 [17]	China	Aminolevulinic acid photodynamic therapy (ALA-PDT)	Minocycline 100 mg	24	2016	3/16 (18.8)	2017	8/20 (47.1)	34	24	

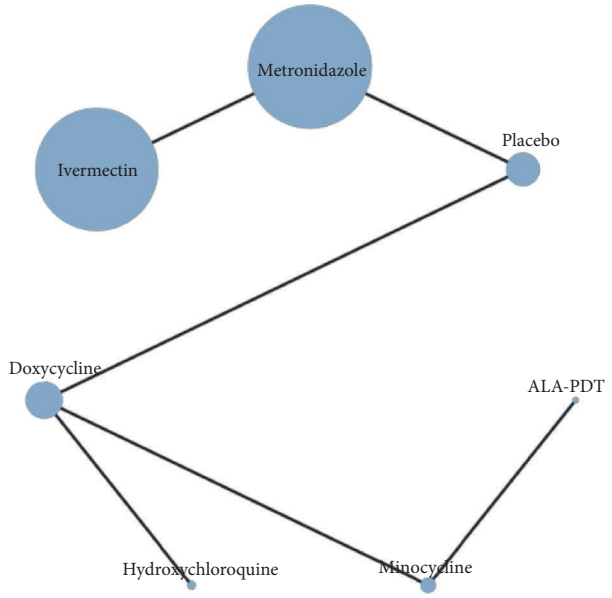

Figure 2: Network plot of the randomized controlled studies comparing the risk of rosacea relapse upon treatment discontinuation.

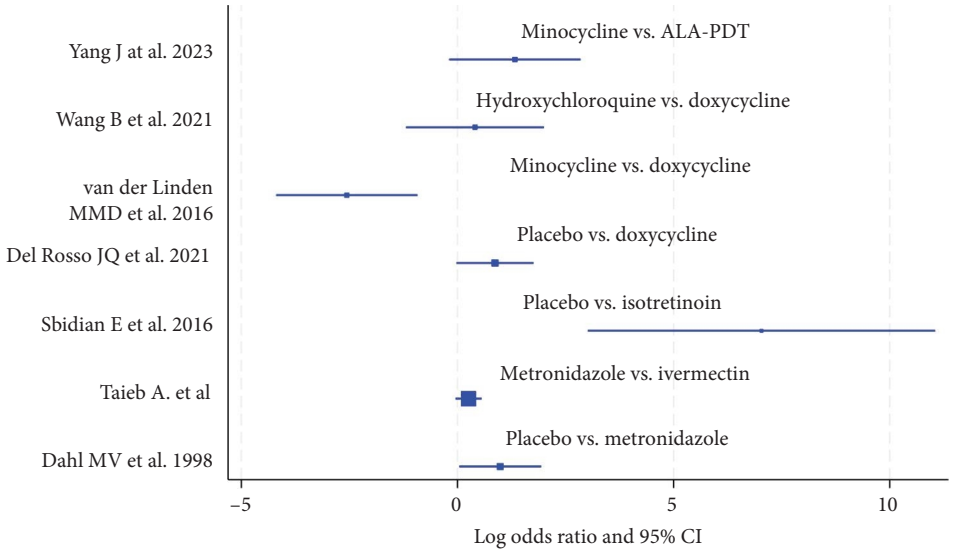

Figure 3: Forest plot of pairwise comparisons of randomized controlled studies comparing the risk of rosacea relapse upon treatment discontinuation.

(range 12–16) for patients treated with metronidazole 0.75% cream.

3.4. Risk of Bias. The results of RoB 2 are summarized in Supporting Figure 2. From funnel plot inspection, we do not find asymmetry suggesting publication bias, as confirmed by the Egger test ($p = 0.065$) (Supporting Figure 3).

3.5. Indirectness. The consistency of different characteristics across the included studies in terms of populations, interventions, and contexts was deemed adequate to consider the reliability of the indirect estimates. However, a high degree of indirectness was found across the included studies (Wald test $p = 0.05$).

4. Discussion

Rosacea is a chronic inflammatory skin condition classically described due to a neurovascular dysregulation associated with an innate immune dysregulation. In particular, cathelicidins (a group of antimicrobial peptides expressed in the skin) and inflammasomes (multiprotein complexes that trigger inflammation) have been implicated in the pathogenesis of rosacea. Recently, evidence of adaptive immune

Table 2: League table showing the results of the network meta-analyses comparing the risk of relapse of rosacea after drug discontinuation as odds ratios (OR) and 95% credible intervals.

ALA-PDT							
48.823 (5.24–454.77)	Doxycycline						
73.23 (4.71–1137.40)	1.50 (0.30–7.39)	Hydroxychloroquine					
0.10 (0–11.08)	0.002 (0–0.13)	0.001 (0–0.12)	Isotretinoin				
33.44 (2.48–450.16)	0.69 (0.18–2.60)	0.46 (0.06–3.65)	325.67 (5.19–20422.65)	Ivermectin			
43.21 (3.27–571.64)	0.89 (0.24–3.25)	0.59 (0.08–4.62)	420.818 (6.78–26102.86)	1.29 (0.96–1.75)	Metronidazole		
3.78 (0.83–17.25)	0.08 (0.02–0.40)	0.05 (0.01–0.51)	36.793 (0.44–3080.36)	0.11 (0.01–0.93)	0.09 (0.01–0.71)	Minocycline	
116.34 (10.53–1285.37)	2.38 (0.98–5.80)	1.59 (0.26–9.86)	1132.97 (20.40–62937.66)	3.48 (1.29–9.40)	2.69 (1.04–6.94)	30.80 (4.79–198.07)	Placebo

Note: OR > 1 means the top-left treatment is better. For example, doxycycline is associated with a lower risk of relapse compared to placebo (OR > 1).
Abbreviation: ALA-PDT, aminolevulinic acid photodynamic therapy.

involvement is emerging, with the participation of Th1 and Th17 subtypes of C4+ T cells [18]. Due to this complex pathogenesis, rosacea often requires combination treatments that sometimes need prolonged or repeated use to achieve disease control.

To date, there are no systematic reviews or meta-analyses about the prevalence and timing of relapse of rosacea in patients treated with topical and systemic drugs. Our meta-analysis provides evidence for the possibility of maintaining remission of rosacea for a certain period of time following drug discontinuation. The meta-analysis involved a total of 7 RCT studies with aggregate data on good responders among 632 moderate/severe papulopustular rosacea patients treated with target therapy and 552 with comparator drugs or placebo. In particular, we found that systemic isotretinoin was the most effective treatment for reducing relapses in patients affected by rosacea, followed by ALA-PDT and minocycline. Among topical drugs, ivermectin and metronidazole appear to reduce the risk of relapse.

A possible reason for isotretinoin's ability to prevent the risk of rosacea relapse is likely related to its long half-life (10–20 h), which allows the drug to remain in the body for an extended period. This prolonged presence enables the medication to continuously exert its effects on sebaceous gland activity and inflammation, which are key contributors to rosacea flare-ups.

Systemic isotretinoin is an off-label treatment for papulopustular rosacea, and it is currently used for cases of resistant disease. Regarding the effectiveness of systemic isotretinoin, it is used as low dose (10 mg/day) [18, 19] as well as intermediate dose (20 mg/day) [19, 20] in clinical practice. Both doses have a similar efficacy and incidence of adverse events while there are different opinions about their impact on relapse [20, 21]. In fact, Erdogan et al. [19, 20] reported that a higher dose of systemic isotretinoin (0.5–1 mg/kg for 3–10 months) prolonged the time of relapse, while other authors reported a higher risk of immediate relapse following the interruption of the drug [21, 22]. The latter advised to introduce systemic isotretinoin at a dosage of 20, 30, and 70 mg/week to reduce the risk of relapse [21, 22].

Topical ivermectin was reported as a well-tolerated and effective treatment for papulopustular rosacea. In the study of Taieb et al. [13], patients treated with topical ivermectin experienced an increased time to first relapse and a reduced relapse rate compared to patients treated with topical metronidazole. In particular, the reported relapse rates were 62.7% for ivermectin and 68.4% for metronidazole at 36 weeks after treatment cessation. The efficacy of ivermectin in preventing disease relapses has been linked to an improved quality of life of patients [22, 23].

The improvement in quality of life can be attributed not only to the delay of the time of relapse but also to a reduced frequency of application of topical antibiotics during the ivermectin therapy and to the association with other topical (e.g., brimonidine) and systemic (e.g., doxycycline) treatments [22, 23]. In a previous nonrandomized and noncontrolled study comparing ivermectin and azelaic acid, topical ivermectin showed later and less relapses than the comparator [23, 24]. In addition, two previous prospective nonrandomized and noncontrolled studies confirmed the low incidence of relapses in patients treated with topical ivermectin [24–26]. Ebbelaar et al. reported relapses in 1 of 6 patients in the "good responders group" (clinical remission after 8 weeks of treatment) and in 1 of 5 patients in the "partial responders group" (8 plus 12 weeks of treatment) [24, 25]. In our previous study which we conducted on patients with mild or moderate rosacea, we found that 45 of the treated patients relapsed with a median time to relapse of 140 days and a mean time of 152 days [25, 26]. Our results show a better efficacy than those reported by Taieb et al.'s study either because patients had a milder form of rosacea or because we considered a shorter follow-up period [13].

Regarding systemic antibiotic therapies, doxycycline 40 mg is the only approved systemic drug for the treatment of papulopustular rosacea [26, 27]. Although doxycycline demonstrated a lower risk of relapse compared with placebo [16] and hydroxychloroquine [15], it did not demonstrate to be more effective than comparators to reach IGA < 1 in our meta-analysis. Doxycycline 100 mg and 40 mg demonstrated the same efficacy on papulopustular rosacea but with a higher number of adverse events in patients treated with the higher dose. Among antibiotic therapies, minocycline 100 mg was associated with greater efficacy and lower relapse rates compared with doxycycline [12].

To prevent relapses, a current proposal is to prescribe a long-term therapy for patients who achieve IGA 0 or IGA 1 scores with a first treatment; this "proactive therapy" may be useful for the maintenance of remission in rosacea. In experts' opinion [27, 28], researchers advise to continue a proactive therapy for at least 9 months in order to prevent or minimize the risk of rosacea flares. The suggested duration and administration schedule of proactive therapy vary among different drugs. Ivermectin cream should be applied daily in the first month after oral antibiotic interruption, followed by alternate-day applications for the next 8 months. It may also be applied on the tarsal border to reduce blepharitis, although this is an off-label indication. Topical azelaic acid 15% gel could be used as an alternative to ivermectin in some cases of oily skin. Low doses of oral isotretinoin could be prescribed for up to a year, in case of severe and persistent papules, even though this is an off-label indication.

This review had numerous limitations. The number of studies included in the review is relatively limited (only 7 studies) because the outcome of interest was rarely reported in RCTs. This result suggests that the definition of "improvement of rosacea" is still not well defined in the literature or that it is not systematically reported in the study. Secondly, a high degree of indirectness could have undermined the external validity of the results. Moreover, we did not consider physical treatments such as laser treatments in our revision.

In conclusion, to date, there have been no systematic reviews or meta-analyses of the prevalence and timing of relapse of rosacea in patients treated with topical and systemic drugs. Our meta-analysis offers evidence suggesting that it is possible to maintain remission of rosacea for a specific duration after stopping treatment. When

comparing the various treatment options, isotretinoin emerged as the one most strongly linked to the lowest likelihood of experiencing a relapse after the medication is discontinued. Further studies are needed to confirm our results.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Disclosure

Contents of the manuscript have not been previously published and are not currently submitted elsewhere.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

Ilaria Trave contributed to conceptualization, data curation, formal analysis, methodology, project administration, resources, software, writing–original draft, and writing–review and editing. Francesco Bellinato contributed to conceptualization, data curation, formal analysis, methodology, project administration, resources, software, writing–original draft, and writing–review and editing. Ilaria Salvi contributed to conceptualization, data curation, methodology, project administration, resources, and writing–review and editing. Andrea Priano contributed to data curation, methodology, and software. Aurora Parodi contributed to writing–review and editing. Paolo Gisondi contributed to data curation, formal analysis, and writing–review and editing. Giampiero Girolomoni contributed to data curation, formal analysis, and writing–review and editing. Emanuele Cozzani contributed to data curation, formal analysis, and writing–review and editing. Ilaria Trave and Francesco Bellinato made an equal contribution to the research.

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The authors have nothing to report.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting Information 1. Supporting Figure 1: SUCRA plot.

Supporting Information 2. Supporting Figure 2: Risk of bias summary (A) and traffic light graph (B) of the studies included in the meta-analysis. A green dot indicates low risk of bias, yellow for unclear risk of bias, and red for high risk of bias. Patients treated with placebo were assumed to be overall in relapse in the study by Sbidian et al. [14].

Supporting Information 3. Supporting Figure 3: Funnel plot.

Supporting Information 4. Supporting Table 1: Clinical features of cases and controls in randomized controlled studies.

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