BJD
British Journal of Dermatology

Interventions for rosacea based on the phenotype approach: an updated systematic review including GRADE assessments*

E.J. van Zuuren,[1] Z. Fedorowicz,[2] J. Tan,[3] M.M.D. van der Linden,[4] B.W.M. Arents,[5] B. Carter[6,7] and L. Charland[8]

[1]Dermatology Department, Leiden University Medical Centre, Leiden, 2333 ZA, the Netherlands
[2]DynaMed Plus, EBSCO Health, 10 Estes Street, Ipswich, MA 01938, U.S.A.
[3]Department of Medicine, University of Western Ontario, London, Canada
[4]Department of Dermatology, Amsterdam University Medical Centre, Amsterdam, the Netherlands
[5]Skin Patients Netherlands (Huidpatiënten Nederland), Nieuwegein, the Netherlands
[6]Biostatistics and Health Informatics, King's College London, London, U.K.
[7]Institute of Psychiatry, Psychology and Neuroscience, London, U.K.
[8]Independent Researcher and Consumer Referee, Quebec, Canada

Linked Comment: Le Cleach and Cribier. Br J Dermatol 2019; **181**:11–12.

Correspondence
Esther J. van Zuuren.
E-mail: e.j.van_zuuren@lumc.nl

Accepted for publication
20 December 2018

Funding sources
Dutch Society for Dermatology and Venereology.

Conflicts of interest
See Appendix 1.

*Plain language summary available online

DOI 10.1111/bjd.17590

Summary

Background Rosacea is a common chronic facial dermatosis. Classification of rosacea has evolved from subtyping to phenotyping.
Objectives To update our systematic review on interventions for rosacea.
Methods We searched CENTRAL, MEDLINE, Embase, LILACS, Science Citation Index and ongoing trials registers (March 2018) for randomized controlled trials. Study selection, data extraction, risk-of-bias assessment and analyses were carried out independently by two authors. Grading of Recommendations, Assessment, Development and Evaluations (GRADE) was used to assess certainty of evidence.
Results We included 152 studies (46 were new), comprising 20 944 participants. Topical interventions included brimonidine, oxymetazoline, metronidazole, azelaic acid, ivermectin and other topical treatments. Systemic interventions included oral antibiotics, combinations with topical treatments or other systemic treatments. Several studies evaluated laser or light-based treatment. We present the most current evidence for rosacea management based on a phenotype-led approach.
Conclusions For reducing temporarily persistent erythema there was high-certainty evidence for topical brimonidine and moderate certainty for topical oxymetazoline; for erythema and mainly telangiectasia there was low-to-moderate-certainty evidence for laser and intense pulsed light therapy. For reducing papules/pustules there was high-certainty evidence for topical azelaic acid and topical ivermectin; moderate-to-high-certainty evidence for doxycycline 40 mg modified release (MR) and isotretinoin; and moderate-certainty evidence for topical metronidazole, and topical minocycline and oral minocycline being equally effective as doxycycline 40 mg MR. There was low-certainty evidence for tetracycline and low-dose minocycline. For ocular rosacea, there was moderate-certainty evidence that oral omega-3 fatty acids were effective and low-certainty evidence for ciclosporin ophthalmic emulsion and doxycycline.

What's already known about this topic?

- Rosacea is a chronic facial inflammatory dermatosis.
- The diagnosis and classification of rosacea have evolved from a subtype approach to a phenotype approach.

- Effective and safe interventions include brimonidine in temporarily reducing persistent erythema; laser- and light-based therapies for mainly telangiectasia; topical azelaic acid, metronidazole and ivermectin, along with oral doxycycline and isotretinoin, for papules/pustules; and topical ciclosporin ophthalmic emulsion for ocular rosacea.

What does this study add?

- A phenotype-based approach with GRADE certainty-of-evidence assessments.
- Topical oxymetazoline reduces temporarily persistent erythema (moderate-certainty evidence).
- There is moderate-certainty evidence that topical minocycline is effective in treating papules/pustules, and oral minocycline is as effective as doxycycline 40 mg modified release.
- Low-dose isotretinoin 0·25 mg kg^{-1} greatly reduces papules/pustules vs. placebo (high-certainty evidence).
- Omega-3 fatty acids improve symptoms of dry eyes and tear gland function (moderate-certainty evidence).

Rosacea is a chronic inflammatory dermatosis affecting the cheeks, nose, eyes, chin and forehead. It is characterized by recurrent episodes of flushing or transient erythema, persistent erythema, papules, pustules and telangiectasia.[1–4] In 2002, the U.S. National Rosacea Society Expert Committee (NRSEC) proposed standardized criteria for the diagnosis and classification of rosacea.[5] They posited that any one of the following primary features in a centrofacial distribution sufficed for diagnosis: flushing, nontransient erythema, papules/pustules or telangiectasia. Secondary features included burning/stinging, erythematous plaques, dry appearance, oedema, peripheral location, phymatous changes and ocular manifestations. Furthermore, they grouped some of these features into four subtypes and one variant: erythematotelangiectatic, papulopustular, phymatous, ocular and granulomatous rosacea (the variant).[5]

However, shortcomings in these diagnostic criteria and subtyping have become apparent.[6] This includes the lack of specificity of some primary features (flushing, papules/pustules, telangiectasia), the exclusion of phyma as a primary feature and the conflation of multiple features into subtypes.[6] For example, the erythematotelangiectatic subtype comprises flushing and persistent central facial erythema with or without telangiectasia, whereas the papulopustular subtype comprises persistent central facial erythema with transient, central facial papules and/or pustules. Thus, both have persistent central facial erythema as a common feature. This has led to confusion in epidemiological research whereby some studies consider them as separate categories, while others aggregate all with central facial erythema as erythematotelangiectatic, a subgroup of which is papulopustular. Furthermore, it does not account for patients presenting with a solitary diagnostic criterion and absence of the others defining a specific subtype. For example, how would one classify a patient with persistent central facial erythema alone but without flushing and telangiectasia? In addition, severity determination of subtypes is complicated by the presence of multiple features each of which may vary in individual severity and responsivity to intervention. However, these individual features were not previously typically evaluated separately. Furthermore, in clinical practice, subtyping may inadequately capture the signs and symptoms of individual patients as some features can extend across subtypes.

Consequently, revised diagnostic criteria have been proposed and recommendations made to abandon the subtyping approach. Both an international rosacea consensus panel and updated NRSEC guidance have recommended harmonized diagnostic criteria and a phenotype-led approach.[6,7] The following features represent independent diagnostic criteria of rosacea: fixed centrofacial erythema that may periodically intensify or phymatous changes. In their absence, diagnosis can also be established by two or more major features: papules/pustules, flushing, telangiectasia, ocular manifestations (lid margin telangiectasia, interpalpebral conjunctival injection, spade-shaped infiltrates in the cornea, scleritis and sclerokeratitis).[7] While secondary features may occur – burning or stinging, oedema, dry appearance – these are not generally considered diagnostic, either alone or in combination. This redirection in diagnosis and elimination of subtypes should provide greater accuracy in diagnosis, establish clearly defined targets for research, facilitate development of severity measures and improve patient-centred care.[7]

Management strategies for people with rosacea should include phenotype-based treatments, in accordance with current classification of rosacea (instead of the previous subtype-classification).[7,8] As rosacea can have an adverse impact on quality of life, these strategies should also be directed towards achieving improvements in general well-being by targeting those aspects most bothersome to the patient.[1,8,9]

The objectives of this systematic review were to examine the different management options and to determine the most effective strategies in the treatment of rosacea. Furthermore, this review more closely aligns evidence-based treatment options with the new phenotype approach.

As the Cochrane Skin Group recently decided to facilitate the regular update of only a few systematic reviews, this update of the Cochrane review is published herein. The content of the full updated review is provided in Appendix S1 (see Supporting Information).

Materials and methods

This updated systematic review conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,[10] and followed a prespecified protocol.[11]

Inclusion criteria

The only inclusion criterion was that the studies were randomized controlled trials (RCTs) examining all types of interventions in people with rosacea.

Outcome measures

Our primary outcomes were quality of life, participant-assessed rosacea severity and proportion of participants reporting an adverse event. Secondary outcome measures were physician-assessed rosacea severity, assessment of erythema and telangiectasia, lesion counts, time to improvement and duration of remission.

Search strategies

We searched several databases up to 6 March 2018: CENTRAL (in The Cochrane Library), MEDLINE, Embase, LILACS and Science Citation Index (for the search strategies see Appendix S1). Furthermore, E.J.v.Z. and M.M.D.v.d.L searched trials registers on 13 March 2018 with the terms 'rosacea' and 'rhinophyma': metaRegister of Controlled Trials (http://www.isrctn.com), U.S. National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov), Australian and New Zealand Clinical Trials Registry (www.anzctr.org.au), World Health Organization International Clinical Trials Registry platform (www.who.int/trialsearch), the Ongoing Skin Trials Register (www.nottingham.ac.uk/ongoingskintrials). Two authors (E.J.v.Z., Z.F.) examined the bibliographies of included and excluded studies for further potentially eligible studies. We did not apply language restrictions and several articles were translated. Two authors independently assessed the titles and abstracts from the searches (E.J.v.Z., Z.F.). The same two authors independently assessed the obtained full-text papers of all potentially eligible included studies. Disagreements were resolved through discussion.

Data extraction and risk-of-bias assessment

Study details and outcome data were collected independently by two authors (E.J.v.Z. and Z.F.) using a piloted data-extraction form. Disagreements on data entry were resolved through discussion. The following details were extracted: design, year of publication, setting, country of origin, number, sex and age of participants, ocular involvement, dropouts and losses to follow-up, intervention, outcomes, baseline data, funding and conflicts of interest. Two authors (E.J.v.Z., Z.F.) independently assessed risk of bias using the Cochrane Collaboration's domain-based assessment tool.[12]

Statistical analysis

We calculated risk ratios (RR) for dichotomous outcomes and mean differences (MD) for continuous outcomes and their associated 95% confidence interval (CI). When RRs were statistically significant, we calculated number needed to treat for one additional beneficial outcome (NNTB) or number needed to treat for one additional harmful outcome (NNTH). In the absence of substantial heterogeneity (I^2 statistic < 60%), data reported for our outcomes were pooled using a random-effects model and summarized with the I^2 statistic. All analyses were undertaken using RevMan 5·3 (The Nordic Cochrane Centre, Copenhagen, Denmark).

Certainty of evidence

We applied Grading of Recommendations, Assessment, Development and Evaluations (GRADE) to assess the certainty of evidence for the prespecified outcomes of the main comparisons using GRADEproGDT (http://gradepro.org) to generate summary-of-findings tables (see Appendix S1 for details on methods, results and 25 summary-of-findings tables).[13] See Table 1 for GRADE Working Group grades of evidence.

Results

Search results

The updated searches identified an additional 219 citations. Trial register searching revealed 38 ongoing studies, totalling

Table 1 GRADE Working Group grades of evidence[a]

High certainty	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]http://gradepro.org

257 references. Fourteen duplicates and 160 references were excluded after examination of titles and abstracts. The remaining 83 studies were assessed for eligibility and only 46 were included (see Fig. 1).[14–57]

Description of the studies

One hundred and fifty-two studies were included (eight references report on two studies),[14–158] comprising 20 944 participants (mean age 48·6 years). More women (n = 12 575) than men (n = 5313) were included; sex was not reported in 3056. Study sample sizes varied from six to 1299 participants, but most were between 30 and 100. The trials were grouped into 12 categories of interventions: topical brimonidine; topical oxymetazoline; topical metronidazole; topical azelaic acid; topical ivermectin; topical metronidazole, azelaic acid and/or other topical treatments in different treatment arms; oral antibiotics; oral antibiotics combined with topical treatments; oral antibiotics compared with topical treatments; other systemic treatments; laser- and light-based therapies; and other treatments or combined treatments.

Full details of all included and excluded studies (starting from the original 2004 review) are available in Appendix S1 (see Supporting Information), sections 'Characteristics of included studies' and 'Characteristics of excluded studies'.

Risk of bias in included studies

Only 16/152 studies were at low risk of bias,[28,33,51,87,93,135,138–140,147,150,155] 52 were assessed as being at high risk of bias and the remaining 84 studies as being at unclear risk of bias (see Fig. 2).

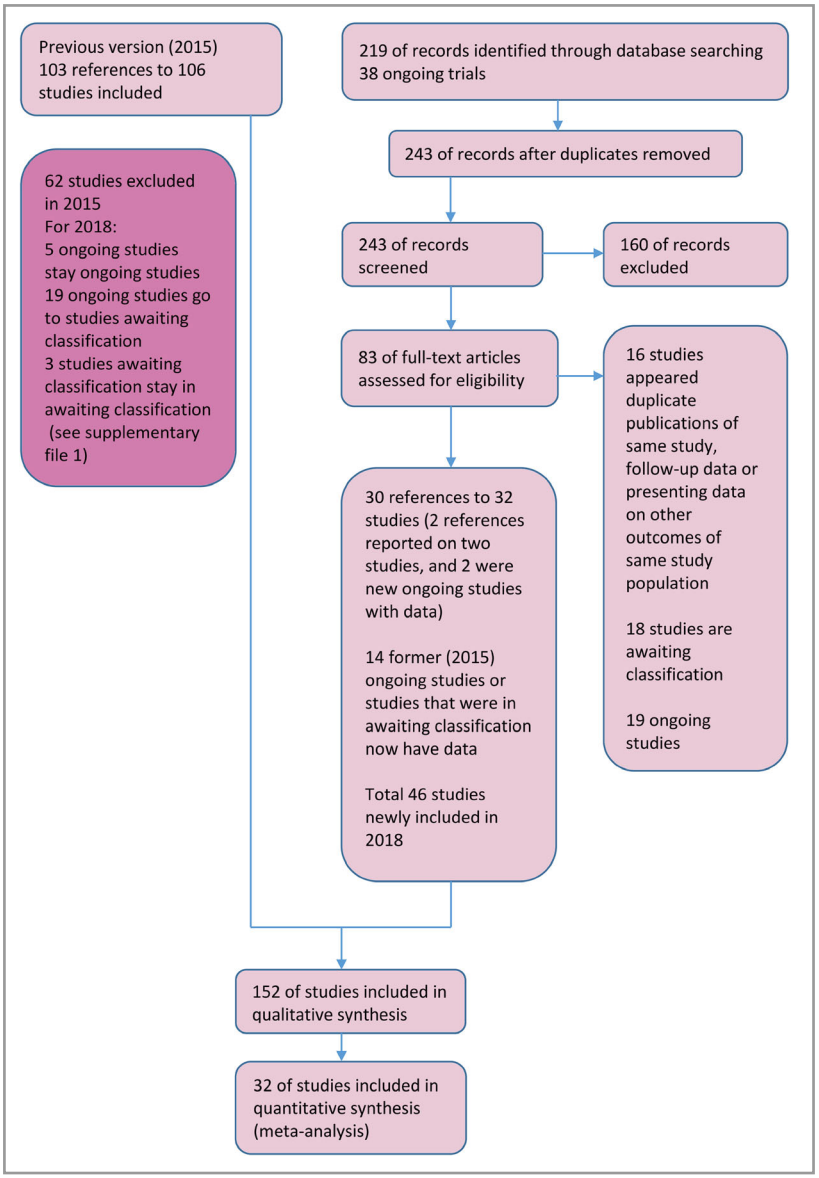

Fig 1. Study flowchart.

Evidence-based treatments

Of the 152 studies, 34 provided no useable or retrievable data that could contribute to the results (see Table 6 in Appendix S1).[46–79] Important reasons were that none of our outcomes was addressed, there were no separate data for rosacea or only limited data were reported in conference abstracts. The remaining 118 studies covered 93 comparisons.

We have summarized pivotal study results in a phenotype-led approach to provide guidance for clinical decision-making, as well as guideline development. Details and results of all 152 studies are reported in Appendix S1.

Treatment of transient erythema and flushing

No RCTs were available.

Treatment of persistent erythema

Brimonidine and oxymetazoline are topical α-adrenergic agonists that induce transient vasoconstriction of cutaneous superficial blood vessels resulting in reduction of facial erythema after application.[15,30,138,139] Both reduce erythema within 30 min, reaching a peak at 3–6 h, after which the effect diminishes and erythema returns to baseline.

Brimonidine Two studies (low risk of bias) showed, after 3 h, a two-grade improvement in patient's self-assessment of erythema (0–4, clear–severe) in 114 of 277 patients using topical brimonidine 3 mg g^{-1} gel vs. 54 of 276 using vehicle [RR 2·11, 95% CI 1·60–2·78 ($P < 0·001$; $I^2 = 0\%$); NNTB 5, 95% CI 3–7; high-certainty evidence].[139] In the brimonidine group adverse events were reported in 88 of 277 participants vs. 68 of 276 in the vehicle group [RR 1·29, 95% CI 0·98–1·69 ($I^2 = 0\%$); moderate-certainty evidence]. In both studies, adverse events were mild and transient. Most frequently reported were worsening of erythema, flushing, pruritus and skin irritation. During the 4-week follow-up, no rebound erythema was observed. Physicians' assessments were in accord with patients' assessments (high-certainty evidence).

Oxymetazoline In two studies (unclear risk of bias) participants' assessments using the subjective self-assessment (0, no signs of unwanted redness; 4, severe redness) showed a two-grade improvement after 3 h in 99 of 446 treated with oxymetazoline 1% cream and in 59 of 439 treated with vehicle [RR 1·65, 95% CI 1·23–2·21 ($P < 0·001$; $I^2 = 0\%$); NNTB 11, 95% CI 7–27; moderate-certainty evidence).[15,30] In the oxymetazoline group 94 adverse events were reported in 446 participants vs. 70 in 439 participants in the vehicle group [RR 1·32, 95% CI 0·97–1·78 ($I^2 = 13\%$); moderate-certainty evidence]. Application-site dermatitis, pruritus and erythema, worsening of inflammatory lesions and headache were the most reported adverse events and were considered mild or moderate in severity. During the 29-day follow-up period six patients in the oxymetazoline group experienced rebound erythema vs. two in the vehicle group. Physicians' assessments were in accord with patients' assessments (moderate-certainty evidence).

Treatment of telangiectasia

Laser- and other light-based therapies Although widely used for reducing erythema and telangiectasia, only a few small-sample-size RCTs (16–49 patients) provided data on laser- and light-based therapies (predominantly low-certainty evidence for various outcomes). There was low-to-moderate-certainty evidence that (long) pulsed dye laser (PDL), neodymium-doped yttrium aluminium garnet (Nd:YAG) laser and intense pulsed light therapy reduce erythema and especially telangiectasia.[131,151] This was supported by several other studies.[40,100,110,144]

Treatment of papules/pustules

Topical azelaic acid Azelaic acid is available as a 15% gel, 20% cream and 15% foam. Seven studies at unclear risk of bias evaluated azelaic acid twice daily vs. vehicle.[20,35,86,90,123,137] Quality of life was addressed in two,[19,136] however, there were no to few differences between groups at the end of the study (high-certainty evidence). In six studies, participant-assessed improvement (marked or excellent) was reached in 648 of 1132 with azelaic acid vs. 439 of 1091 with vehicle [RR 1·40, 95% CI 1·28–1·53 ($P < 0·001$; $I^2 = 0\%$); NNTB 6, 95% CI 5–8].[20,35,86,123,137] These results were comparable with physicians' assessments (both high-certainty evidence). There was little-to-no difference in the number of participants experiencing an adverse event: 200 of 799 on azelaic acid vs. 143 of 760 with vehicle [four studies: RR 1·29, 95% CI 0·92–1·81 ($I^2 = 46\%$); moderate-certainty evidence].[20,35,86,137] Adverse events were transient, mild-to-moderate intensity, with burning, stinging or irritation most commonly reported. In three studies the lesion count reduction was 10–11 with vehicle, indicating a treatment effect, but the MD favoured azelaic acid [−3·00 lesions, 95% CI −4·13 to −1·86 ($P < 0·001$; $I^2 = 9\%$); high-certainty evidence].[20,35,137] Azelaic acid reduced erythema slightly (physician-assessed, high-certainty evidence).[35,86,90,123,137]

Topical ivermectin Two studies at low risk of bias compared topical ivermectin 1% cream once daily with vehicle.[155] More participants in the ivermectin group (n = 467/910) experienced improvements in quality of life than in the vehicle groups (n = 153/461), and at end of the study patients considered rosacea had 'no [negative] effect on their overall quality of life' [RR 1·55, 95% CI 1·34–1·79 ($P < 0·001$; $I^2 = 0\%$); NNTB 6, 95% CI 4–8; high-certainty evidence]. Good-to-excellent improvement was reported by 615 of 910 participants with ivermectin vs.169 of 461 with vehicle [RR 1·84, 95% CI 1·62–2·09 ($P < 0·001$; $I^2 = 0\%$); NNTB 3, 95% CI 3–4; high-certainty evidence] and physicians' assessments were in concordance (moderate-certainty evidence). There was no difference in the number of participants experiencing

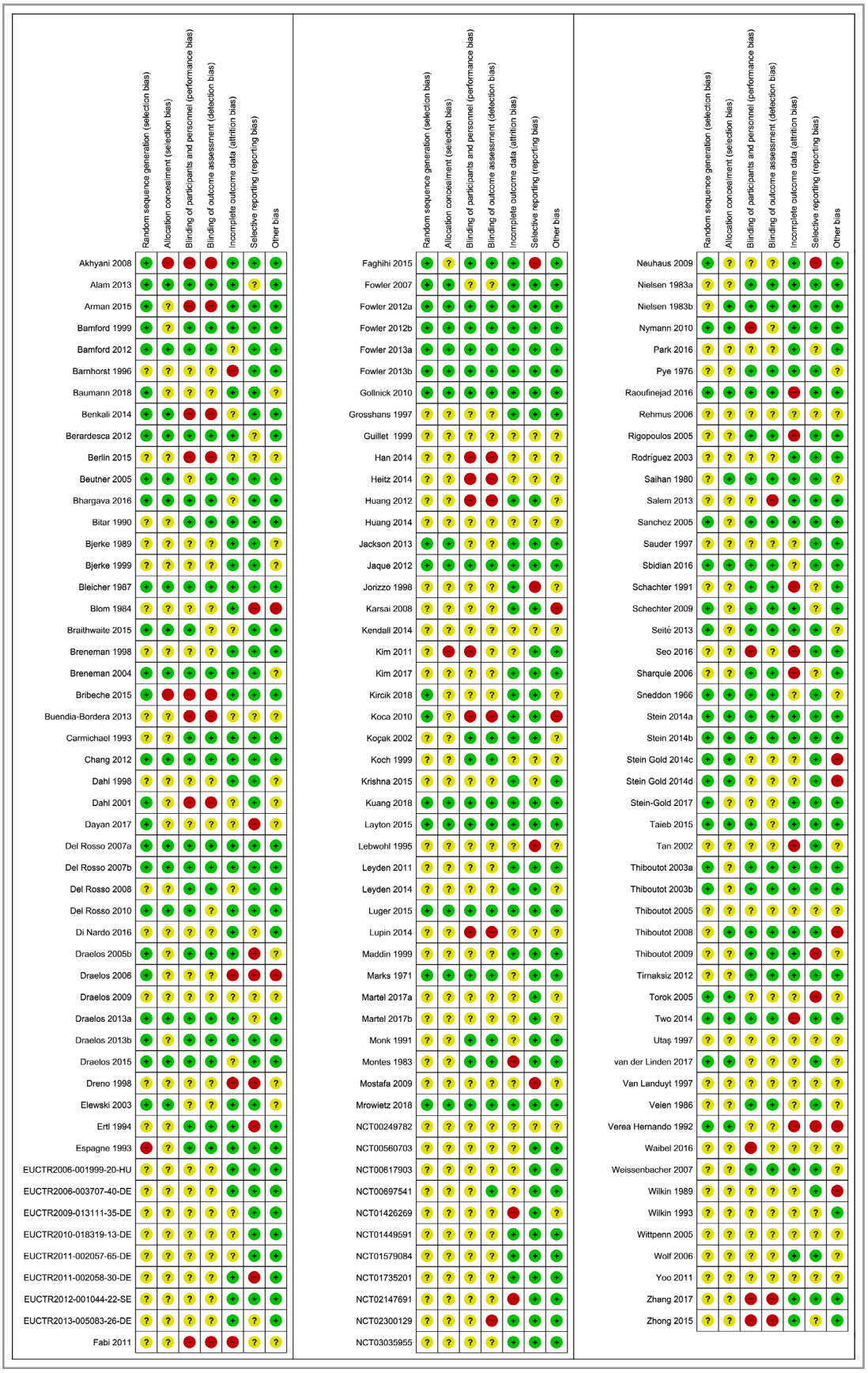

Fig 2. Risk-of-bias summary.

an adverse event [n = 62/1050 with ivermectin vs. n = 45/567 with vehicle (RR 0·83, 95% CI 0·54–1·28; I^2 = 26%; moderate-certainty evidence].[24,155] Skin burning, pruritus and dry skin were most frequently reported. Reductions in lesion counts (three studies) were most 20 and 27 with ivermectin and between 12 and 23 with vehicle, with a MD between groups of −8·09 lesions [95% CI −9·82 to −6·35 (P < 0·001; I^2 = 52%); high-certainty evidence], again showing treatment effect of the vehicle.[24,155]

Topical metronidazole Topical metronidazole is available as 0·75% gel and 1% cream. Nine trials at low-to-high risk of bias compared metronidazole with placebo.[82–85,87,88,91,103,111] Data from three studies could not be pooled for participants' assessments owing to substantial heterogeneity (65%) but indicated that metronidazole was more effective than placebo (low-certainty evidence), which was in line with physicians' assessments of 94/195 improving with metronidazole and 40/139 with placebo [RR 1·98, 95% CI 1·29–3·02 (P = 0·002; I^2 = 44%); moderate-certainty evidence].[85,88,111] Data from six studies showed that 379 of 1375 participants reported an adverse event with metronidazole vs. 64 of 398 with placebo [RR 1·19, 95% CI 0·94–1·51 (I^2 = 0%); moderate-certainty evidence].[83–85,88,103,111] Adverse events were mild, consisting of pruritus, skin irritation and dry skin. No SDs were provided for lesion counts and erythema; data were skewed but appeared to support those reported as physician-assessed improvement (both moderate-certainty evidence).

Topical azelaic acid versus topical metronidazole Three studies at unclear risk of bias (total of 451 participants) reported contradictory data for this comparison (moderate-certainty evidence).[97,105,130] Azelaic acid might be slightly more beneficial than metronidazole (according to participants and physicians), but the difference may not be important. Azelaic acid likely results in a small and possibly unimportant increase in adverse events when compared with topical metronidazole. Reductions in lesion counts were comparable in both groups.

Topical ivermectin versus topical metronidazole Topical ivermectin 1% cream once daily likely improved quality of life slightly more than topical metronidazole 0·75% twice daily, based on one study at low risk of bias with 962 patients [RR 1·11, 95% CI 1·01–1·21 (P = 0·02); NNTB 15, 95% CI 8–100; moderate-certainty evidence].[156] Reduction in Dermatology Life Quality Index was 5·18 in the topical ivermectin group and 3·92 in the topical metronidazole group [both meeting minimal important difference (MID)].[159,160] Good-to-excellent improvement based on participants' assessments was reported by 409 of 478 with ivermectin vs. 362 of 484 with metronidazole [RR 1·14, 95% CI 1·07–1·22 (P < 0·001); NNTB 10, 95% CI 7–17; moderate-certainty evidence].[156] There was no difference in number of participants reporting an adverse event. Physicians' assessments in two studies were in concordance with participants' assessments.[20,155] Mean ± SD reduction in lesion count was 27·70 ± 8·85 with ivermectin vs. 23·60 ± 8·23 with metronidazole [MD −4·10, 95% CI −5·18 to −3·02 (P < 0·001); high-certainty evidence].[156]

Minocycline foam Minocycline foam (1·5%, 3% vs. vehicle) was evaluated in a 12-week study at low risk of bias including 232 participants.[33] Reductions in overall rosacea quality-of-life index (RosaQoL) score was 0·4 with minocycline vs. 0·2 with vehicle. The investigators reported the P-value as 0·003, but as RosaQoL MID has not been established, the data are difficult to interpret. Mean ± SD lesion count reduction was 21·1 ± 8·1 with minocycline vs. 7·8 ± 8·0 with vehicle (MD −13·30, 95% CI −15·82 to −10·78). Investigator's Global Assessment (IGA) supported these results. In the minocycline foam group, 46 of 79 reported an adverse event vs. 31 of 78 with vehicle [RR 1·47, 95% CI 1·05–2·04 (P = 0·02); NNTH 5, 95% CI 3–32]. Minocycline-related adverse events were eczema, burning sensation or worsening rosacea. There was moderate-certainty evidence for all outcomes.

Clindamycin cream or gel Two studies at unclear risk of bias (629 participants) indicated clindamycin 1% cream or gel twice daily was not more effective than vehicle for any of the outcomes (low-to-moderate-certainty evidence).[32]

Clindamycin combined with tretinoin gel One study at low risk of bias with 87 participants evaluated the combination of clindamycin phosphate 1·2% with tretinoin 0·025% in a gel vs. placebo.[135] No differences between groups were seen for quality of life, physician assessments, erythema and lesion counts, but there were more adverse events in the active treatment group, such as dry skin, scaling and worsening of rosacea. There was moderate-certainty evidence for all outcomes.

Remaining topical treatments Studies evaluating permethrin, dapsone, sodium sulfacetamide with sulfur, pimecrolimus and some more unusual treatments (e.g. tranexamic acid, P-3075 cream, SEI003 cream, praziquantel ointment, diclofenac sodium gel, incobotulinumtoxinA injections, kanuka honey) were at unclear-to-high risk of bias, inadequately reported or provided very limited data, but are addressed in Appendix S1.

Oral tetracyclines Two short studies (4 and 6 weeks' duration, respectively), at unclear risk of bias, including a total of 151 participants compared oral tetracycline 250 mg twice daily with placebo.[106,121] The certainty of evidence was low for all outcomes. Tetracycline may result in a large reduction in lesion count, which is supported by physician-assessed improvement in rosacea severity. However, patients considered there was no difference in effectiveness between tetracycline and placebo.[106]

Two studies at low risk of bias and two studies at unclear risk of bias assessed doxycycline 40 mg modified release (MR) vs. placebo.[19,34,93] None assessed participant-assessed rosacea severity. There was high-certainty evidence that more participants with doxycycline 40 mg MR achieved 'clear' or 'almost clear' (n = 91/353) on the IGA than with placebo

(n = 53/354) [RR 1·69, 95% CI 1·26–2·28 (P < 0·001; I^2 = 0%); NNTB 9, 95% CI 6–20].[19,93] One study was excluded from pooling (I^2 = 70%) owing to lower number of lesions at baseline.[19] The MD of pooled data was −5·51 lesions [95% CI −7·81 to −3·21 (P < 0·001); I^2 = 0%; moderate-certainty evidence].[93] Doxycycline 40 mg MR probably reduced erythema slightly based on three studies and was assessed with the Clinician's Erythema Assessment [MD −0·48, 95% CI −0·97 to 0·00 (P = 0·05; I^2 = 28%); moderate-certainty evidence].[19,93] Slightly more adverse events occurred with doxycycline 40 mg MR (RR 1·27, 95% CI 1·08–1·49; moderate-certainty evidence), but the majority was considered mild or moderate in both groups.[19,34,93]

Low-certainty evidence from one study (91 participants) at unclear risk of bias showed that 40 mg MR doxycycline is at least as effective as 100 mg, with fewer side-effects.[94]

A noninferiority study of minocycline 100 mg with doxycycline 40 mg MR was assessed as being at unclear risk of bias.[43] Patients' assessments showed that 22 of 40 participants with minocycline achieved excellent or good improvement vs. 20 of 40 in the doxycycline 40 mg MR group (RR 1·10, 95% CI 0·72–1·67; low-certainty evidence). These findings were in accordance with lesion count reductions. Quality of life was assessed using RosaQol and the MD was −0·24 [95% CI −0·30 to −0·18; P < 0·001; low-certainty evidence], a small and possibly unimportant difference favouring minocycline. Physicians' assessments based on IGA (clear or near clear) favoured minocycline [RR 3·43, 95% CI 1·67–7·04 (P < 0·001); NNTB 2, 95% CI 2–4; high-certainty evidence]. There was no difference in the number of patients experiencing an adverse event (RR 1·17, 95% CI 0·83–1·65; low-certainty evidence) with the adverse events being similar (e.g. gastrointestinal side-effects and headache).

In one study (unclear risk of bias) with 60 participants, minocycline 45 mg with or without topical azelaic acid demonstrated similar effectiveness in reducing inflammatory lesions 2013) (low certainty of evidence).[142] There was a reduction of 11–12 lesions in both treatment arms.

Azithromycin versus doxycycline Azithromycin 500 mg three times a week (and then tapered) vs. doxycycline 100 mg daily was evaluated in one study at high risk of bias (67 participants).[80] There were no differences in effectiveness and safety for any of the outcomes (very-low-certainty evidence). Both treatments reduced inflammatory lesions by 16–18 lesions within 3 months.

Isotretinoin versus placebo Low-dose isotretinoin 0·25 mg kg^{-1} was compared with placebo over 4 months in difficult-to-treat 'papulopustular' rosacea (cyclin-refractory or frequently relapsing) in a study at unclear risk of bias.[39] After 4 months, participants assessed satisfaction on a visual analogue scale of 0–100 (higher score being better) showed a median score of 80 in the isotretinoin group vs. a score of 9 in the placebo group (low-certainty evidence). Isotretinoin likely improves quality of life, as measured with the Skindex (moderate-certainty evidence), with scores showing median relative variations of −49·4% in the isotretinoin-treated group (108 participants) vs. −18·0% in the placebo group (48 participants) (investigators reported a P-value of 0·002). Sixty-two of 108 (57·4%) patients treated with isotretinoin achieved a 90% reduction in inflammatory lesion count vs. five of 48 (10·4%) in the placebo group [RR 5·51, 95% CI 2·37–12·83 (P < 0·001); NNTB 2, 95% CI 2–3; high-certainty evidence]. The median reduction in lesion count was 13 (92% reduction) in the isotretinoin-treated group and six lesions in the placebo group (36%). This was supported by the physicians' assessments. Treatment-related adverse events were more frequently reported in the group treated with isotretinoin [75/108 (69%)] than with placebo [21/48 (44%)] [RR 1·59, 95% CI 1·12–2·24 (P = 0·009); NNTH 4, 95% CI 2–11; moderate-certainty evidence]. Eczema, cheilitis, dry skin, abdominal pain, myalgias/arthralgias and dry eyes, which are well-known side-effects of isotretinoin, were reported in the active treatment group.

Isotretinoin versus doxycycline One study at low risk of bias examined low-dose isotretinoin 0·3 mg kg^{-1} vs. doxycycline 100 mg for 14 days and then tapered to 50 mg.[140] A small difference in favour of isotretinoin was observed in participants' assessments (total of 261 participants) of good-to-excellent improvements [RR 1·23, 95% CI 1·05–1·43 (P = 0·009); NNTB 7, 95% CI 4–25], in lesion count reduction (MD −3, 95% CI −5·18 to −0·82; P = 0·007) and physicians' assessments of marked improvement or complete remission [RR 1·18, 95% CI 1·03–1·36 (P = 0·02); NNTB 9, 95% CI 5–50]. There was no difference in the number of patients (299 in total) experiencing an adverse event (RR 1·19, 95% CI 0·74–1·92). Certainty of evidence was moderate for these outcomes. There was high-certainty evidence of no difference in improvement of erythema or telangiectasia.

Remaining systemic treatments Results on other systemic treatments are discussed in Appendix S1.

Treatment for phyma

Surgical therapies including ablative laser therapies have been used with reportedly good results for clinically noninflamed phyma, but no eligible RCTs were identified. For clinically inflamed phymas both doxycycline and isotretinoin are recommended, but no supporting evidence based on RCTs is available.[8]

Treatment for ocular features

One study (unclear risk of bias) with 37 patients showed that ciclosporin ophthalmic emulsion 0·05% twice daily improved quality of life vs. artificial tears, as assessed with the Ocular Surface Disease Index (OSDI) (scale 0–100, 100 = worst).[119] MD after 3 months was −8·6 (95% CI −15·42 to −1·78; P = 0·01). Physicians used the Schirmer test, which gave a MD of 4·1 mm (95% CI 1·66–6·54; P = 0·001), confirming

improved tear production and increased tear break-up time (TBUT) (MD 3·6 s, 95% CI 2·59–4·61; P < 0·001). There was no difference in number of participants with an adverse event. There was low-certainty evidence for all outcomes.

Ciclosporin ophthalmic emulsion twice daily was compared with doxycycline 100 mg twice daily for the first month followed by 2 months once daily in a study at high risk of bias (38 participants).[14] Quality of life assessed with the OSDI has an MD of −8·81 (95% CI −14·32 to −3·32; P = 0·002) favouring ciclosporin ophthalmic emulsion. This was confirmed by patients' assessments based on a symptom score (0–9, higher = worse) with a MD of −1·85 (95% CI −2·60 to −1·10; P < 0·001). The Schirmer test (MD 2·11 mm, 95% CI 0·82–3·40; P = 0·001), TBUT (MD 2·32, 95% CI 0·81–3·83; P = 0·003), eyelid score and cornea/conjunctival sign score all favoured ciclosporin ophthalmic emulsion. There was low-certainty evidence for all outcomes.

One study at unclear risk of bias (130 participants) evaluated omega-3 fatty acids (180 mg eicosapentaenoic acid and 120 mg docosahexaenoic acid) one capsule twice daily vs. placebo twice daily for dry eyes in rosacea.[16] There was moderate-certainty evidence for all outcomes. Participants used the Dry Eye questionnaire and Scoring System to evaluate this outcome (0–6 mild, 6·1–12 moderate, 12·1–18 severely symptomatic dry eye). The mean ± SD change from baseline was −5·30 ± 1·52 in the 65 participants treated with omega-3 fatty acids vs. −0·20 ± 1·59 in the 65 participants treated with placebo (MD −5·10, 95% CI −5·63 to −4·57; P < 0·001). The MD of the Schirmer test (MD 1·70 mm, 95% CI 0·62–2·78; P = 0·002), TBUT (MD 3·30 s, 95% CI 2·86–3·74; P < 0·001) and Meibomian gland score (lower score is better) (MD −1·28, 95% CI −1·53 to −1·03; P < 0·001) all favoured omega-3 fatty acids.

Combination of treatments

One study (unclear risk of bias) with 190 patients examined the combination of brimonidine 0·33% gel in the morning with ivermectin 1% cream in the evening (to address both persistent erythema and papules/pustules) vs. vehicles.[42] According to participants' assessments (good or excellent) [RR 1·42, 95% CI 1·12–1·80 (P = 0·004); NNTB 4, 95% CI 3–13] and the Physician's Global Assessment (clear or almost clear) [RR 1·66, 95% CI 1·18–2·35 (P = 0·004); NNTB 4, 95% CI 2–13], combined treatment was effective in treating both features, with reported reductions of erythema [RR 1·84, 95% CI 1·38–2·46 (P < 0·001); NNTB 3, 95% CI 2–5] and papules/pustules. The percentage reduction from baseline was 78·3% for the active treatment group vs. 65·5% for the vehicles group.

One study, assessed at unclear risk of bias, of 72 participants that examined combining doxycycline 40 mg MR with topical metronidazole vs. metronidazole alone was not specifically designed to treat more than one feature (focusing on papules/pustules rather than on erythema).[98] The results of this study indicated that combining treatments had a beneficial effect on more than one feature.

Maintenance treatments

Three RCTs addressed the effectiveness of combined maintenance treatments following disease control. Topical metronidazole 0·75%, ivermectin 1% and azelaic acid 15% gel seemed effective and safe for maintenance therapy.[41,91]

Discussion

This updated review, including 152 studies, focused on studies and comparisons that were likely to provide evidence-based and reliable treatment options, within a phenotype approach.

For transient reduction of persistent erythema, there is high-certainty evidence to support the efficacy and safety of brimonidine gel and moderate-certainty evidence for oxymetazoline cream during 12 h after application. Both topical treatments probably result in little-to-no difference in number of participants experiencing an adverse event when compared with vehicle (moderate-certainty evidence).

For persistent erythema and telangiectasia, there was low-to-moderate-certainty evidence of the efficacy of (long) PDL, Nd:YAG laser and intense pulsed light therapy.

For papules/pustules of rosacea, there is high-certainty evidence that topical azelaic acid and topical ivermectin reduce lesion counts, and moderate-certainty evidence for topical metronidazole and topical minocycline. It still needs to be established whether topical azelaic acid is more effective than topical metronidazole, but topical ivermectin appeared to be slightly more effective than topical metronidazole (moderate-certainty evidence).

As for systemic treatments of papules/pustules, there is low-certainty evidence that tetracycline is effective and moderate-certainty evidence for doxycycline (40 mg MR). There is low-certainty evidence that 40 mg MR doxycycline is at least as effective as 100 mg, with fewer adverse events with 40 mg MR. The evidence for the efficacy and safety of low-dose minocycline 45 mg is of low certainty and of very low certainty for azithromycin. There is probably little-to-no difference between minocycline 100 mg and doxycycline 40 mg MR (moderate-certainty evidence). Serious adverse events have been reported in rare cases with minocycline, such as autoimmune hepatitis, lupus erythematosus and hyperpigmentation of the skin and tissues.[4] Low-dose isotretinoin 0·25 mg kg^{-1} results in far more participants with a minimum 90% lesion count reduction when compared with placebo (high-certainty evidence). Isotretinoin is known to be teratogenic and should therefore not be prescribed to pregnant women or women who are trying to become pregnant.[4] Compared with doxycycline (100 mg tapered to 50 mg after 2 weeks), low-dose isotretinoin 0·3 mg kg^{-1} probably results in a small effect, but that difference in reducing lesion counts may not be important. Both oral

isotretinoin and oral doxycycline showed important reductions in lesion counts (moderate-certainty evidence).

For most treatments, or combinations thereof, there is no clear evidence favouring any with regard to higher remission rates or fewer adverse events. However, more participants experienced an adverse event with topical azelaic acid, topical minocycline and oral isotretinoin, when compared with vehicle or placebo.

No studies could be included that addressed treatment of phymatous rosacea.

For ocular rosacea, ciclosporin 0·05% ophthalmic emulsion was shown to be more beneficial than artificial tears (low-certainty evidence). Ciclosporin 0·05% was also more effective than doxycycline 200 mg for the first month and 100 mg for the following 2 months for all the addressed outcomes (low-certainty evidence). Omega-3 fatty acids improved symptoms of dry eyes and improved tear gland function (moderate-certainty evidence).

One study demonstrated that a combination of brimonidine gel in the morning and ivermectin cream in the evening was effective in treating both erythema and papules/pustules vs. vehicles.[42]

Topical metronidazole 0·75%, ivermectin 1% and azelaic acid 15% gel seem effective and safe as maintenance treatments regarding papules/pustules. Other maintenance treatments for rosacea have not been addressed in RCTs.

Since the last update of this review in 2015,[161] a number of other reviews or guidelines have been published.[162–166] The Canadian Clinical Practice guidelines for rosacea, published in 2016, used the 2015 version of this review as a source of clinical evidence and basis for making recommendations using the GRADE approach.[162]

A Swiss S1 guideline for the treatment of rosacea has been published in which assessments of evidence (A–E) were used, and 13 national experts on rosacea reached consensus on recommendations.[163] They concluded that there was level A evidence (no major design flaws and at least one double-blind RCT) for pimecrolimus, topic retinoids, topical permethrin, topical benzoyl peroxide/clindamycin, topical erythromycin and topical dapsone, oral zinc sulfate and oral ampicillin, on which we clearly disagree. There were no details on inclusion criteria for studies, neither basis of appraisal of quality nor judgements on the risk of bias. No patients or patient-advocacy groups were included and the guideline appeared solely reliant on the contribution of expert panels. In contrast, and in terms of recognizing the significant impact of this condition on patients, we have tried to ensure that we received timely, patient-relevant input at all stages of conducting and reporting this review, and have included two patients as co-authors. Furthermore, we applied the widely adopted GRADE approach to rate the certainty of evidence for our predefined outcomes of the most clinically relevant comparisons.

The global ROSacea COnsensus panel (ROSCO), an international panel of dermatologists and ophthalmologists developed recommendations for diagnosis, classification and treating rosacea, on a phenotype rather than subtype approach.[6,8] The classification recommendations from that consensus were adopted in this update.

Three reviews on topical ivermectin in rosacea have been published.[164–166] One was a narrative review describing the pharmacological properties of ivermectin and available data on efficacy and tolerability.[164] Another was a systematic review with clinical guideline recommendations in which the Jadad score (randomization, double blinding and dropouts) was used to assess risk of bias but was not a key criterion (concealment of treatment allocation).[165] Nevertheless, their conclusions are in concordance with those in this review. As head-to-head studies comparing various topical treatments are generally lacking, a network meta-analysis comparing the efficacy, safety and tolerability of topical ivermectin with other currently available topical agents has been conducted.[166] This study expanded and built upon earlier versions of our review,[161,167] and was conducted and reported robustly. The authors concluded that topical ivermectin appeared to be more effective than other topical treatment options for papules/pustules of rosacea, with similar safety and tolerability.

Limitations of our review were that the lack of response from investigators regarding missing trial details largely resulted in less favourable risk-of-bias assessments (unclear as opposed to low risk). Unfortunately, our outcomes of time to improvement and duration of remission were not or minimally addressed in the studies. The lack of standardized and validated scales was challenging for pooling data. Scales should be developed with greater focus on specific features rather than conflation of multiple features into a single scale, as previously done with the subtype approach. This focus will provide greater clarity on the effect of interventions on distinct rosacea features. As an example, this would avoid the current conundrum of extracting the effect on persistent erythema versus perilesional erythema of inflammatory lesions in studies on 'papulopustular rosacea'.

In conclusion, we have summarized the data and most pivotal comparisons of RCTs for rosacea in a phenotype-led approach providing certainty of evidence for predefined outcomes. Appendix S1 provides the complete and latest updated version of the systematic review 'Interventions for rosacea', which includes all 93 comparisons, including 25 summary-of-findings tables. This review can therefore be the basis for developing or updating evidence-based guidelines and for guidance in clinical decision-making.

Acknowledgments

We would like to thank librarian Jan Schoones, Walaeus Library of Leiden University Medical Centre, for his help with searching for the trials. We would also like to thank Na Luo, from the Department of Dermatology Southwest Hospital Army Medical University Chongqing, China, and Xiamomeng Liu, Department of Dermatology, Flevo Hospital Almere, the Netherlands, for her translation of the study by Zhang *et al.* from Chinese into English.[44]

References

1 Elewski BE, Draelos Z, Dréno B *et al.* Rosacea – global diversity and optimized outcome: proposed international consensus from the Rosacea International Expert Group. *J Eur Acad Dermatol Venereol* 2011; **25**:188–200.

2 Korting HC, Schöllmann C. Current topical and systemic approaches to treatment of rosacea. *J Eur Acad Dermatol Venereol* 2009; **23**:876–82.

3 Marks R. The enigma of rosacea. *J Dermatolog Treat* 2007; **18**:326–8.

4 van Zuuren EJ. Rosacea. *N Engl J Med* 2017; **377**:1754–64.

5 Wilkin J, Dahl M, Detmar M *et al.* Standard classification of rosacea: report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. *J Am Acad of Dermatol* 2002; **46**:584–7.

6 Tan J, Alemeida LM, Bewley A *et al.* Updating the diagnosis, classification and assessment of rosacea: recommendations from the global ROSacea COnsensus (ROSCO) panel. *Br J Dermatol* 2016; **17**:431–8.

7 Gallo RL, Granstein RD, Kang S *et al.* Standard classification and pathophysiology of rosacea: the 2017 update by the National Rosacea Society Expert Committee. *J Am Acad Dermatol* 2018; **78**:148–55.

8 Schaller M, Almeida LM, Bewley A *et al.* Rosacea treatment update: recommendations from the global ROSacea COnsensus (ROSCO) panel. *Br J Dermatol* 2017; **176**:465–71.

9 Bikowski JB, Goldman MP. Rosacea: where are we now? *J Drugs Dermatol* 2004; **3**:251–61.

10 Liberati A, Altman DG, Tetzlaff J *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; **339**:b2700.

11 van Zuuren EJ, Powell FC, Graber M. Interventions for rosacea [Protocol]. *Cochrane Database Syst Rev* 2000; **12**:CD003262.

12 Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions* 5.1.0. Available at: www.cochrane-handbook.org (last accessed 12 September 2018).

13 Schünemann H, Brozek J, Guyatt G, Oxman A, editors. *GRADE Handbook for Grading Quality of Evidence and Strength of Recommendations*. Updated October 2013. The GRADE Working Group, 2013. Available at: https://gdt.gradepro.org/app/handbook/handbook.html (last accessed 5 February 2019).

14 Arman A, Demirseren DD, Takmaz T. Treatment of ocular rosacea: comparative study of topical cyclosporine and oral doxycycline. *Int Journal Ophthalmol* 2015; **8**:544–9.

15 Baumann L, Goldberg DJ, Stein Gold L *et al.* Pivotal trial of the efficacy and safety of oxymetazoline cream 1.0% for the treatment of persistent facial erythema associated with rosacea: findings from the second REVEAL trial. *J Drugs Dermatol* 2018; **17**:290–8.

16 Bhargava R, Chandra M, Bansal U *et al.* A randomized controlled trial of omega 3 fatty acids in rosacea patients with dry eye symptoms. *Curr Eye Res* 2016; **41**:1274–80.

17 Braithwaite I, Hunt A, Riley J *et al.* Randomised controlled trial of topical kanuka honey for the treatment of rosacea. *BMJ Open* 2015; **5**:e007651.

18 Dayan S, Ashourian N, Cho K. A pilot, double-blind, placebo-controlled study to assess the efficacy and safety of incobotulinumtoxinA injections in the treatment of rosacea. *J Drugs Dermatol* 2017; **16**:549–54.

19 Di Nardo A, Holmes AD, Muto Y *et al.* Improved clinical outcome and biomarkers in adults with papulopustular rosacea treated with doxycycline modified-release capsules in a randomized trial. *J Am Acad Dermatol* 2016; **74**:1086–92.

20 Draelos ZD, Elewski BE, Harper JC *et al.* A phase 3 randomized, double-blind, vehicle-controlled trial of azelaic acid foam 15% in the treatment of papulopustular rosacea. *Cutis* 2015; **96**:54–61.

21 EUCTR2006-001999-20-HU. Assessment of the efficacy and safety of three concentration:1%, 0.3%, 0.1% of CD5024 cream once daily and CD5024 1% cream twice daily, versus its vehicle and versus metronidazole cream (Rozex®) in patients with papulopustular rosacea over 12 weeks. Available at: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2006-001999-20-HU (last accessed 13 September 2018).

22 EUCTR2006-003707-40-DE. Activity of twice daily per os administration of CD06713 at 8 mg versus its placebo during 4 weeks treatment, in patients with erythemato-telangiectatic rosacea. Available at: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2006-003707-40-DE (last accessed 13 September 2018).

23 EUCTR2009-013111-35-DE. Effect of CD08514 versus placebo, in patients presenting with type 1 rosacea, over an 8-week treatment. Available at: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2009-013111-35-DE (last accessed 13 September 2018).

24 EUCTR2010-018319-13-DE. A double-blind, vehicle controlled, parallel group study assessing the activity of CD5024 1% cream in subjects with papulopustular rosacea over 12 weeks treatment. Available at: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2010-018319-13-DE (last accessed 13 September 2018).

25 EUCTR2011-002057-65-DE. Effect of CD08100/02 3% gel versus placebo in subjects presenting with erythematotelangiectatic rosacea over a 4 week treatment period. Available at: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011-002057-65-DE (last accessed 13 September 2018).

26 EUCTR2012-001044-22-SE. A multicenter, randomized, double-blind, vehicle-controlled, parallel group study to demonstrate the efficacy and assess the safety of CD07805/47 gel 0.5% applied topically once daily in subjects with moderate to severe facial erythema of rosacea. Available at: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2012-001044-22-SE (last accessed 13 September 2018).

27 Faghihi G, Khosravani P, Nilforoushzadeh MA *et al.* Dapsone gel in the treatment of papulopustular rosacea: a double-blind randomized clinical trial. *J Drugs Dermatol* 2015; **14**:602–6.

28 Jaque AS, Vera CK. Timolol tópico en el tratamiento de rosácea eritematotelangiectásica. Ensayo clínico randomizado doble ciego. *Rev Chilena Dermatol* 2012; **28**:418–30.

29 Kim SJ, Lee Y, Seo YJ *et al.* Comparative efficacy of radiofrequency and pulsed dye laser in the treatment of rosacea. *Dermatol Surg* 2017; **43**:204–9.

30 Kircik LH, DuBois J, Draelos ZD *et al.* Pivotal trial of the efficacy and safety of oxymetazoline cream 1.0% for the treatment of persistent facial erythema associated with rosacea: findings from the first REVEAL trial. *J Drugs Dermatol* 2018; **17**:97–105.

31 Krishna R, Guo Y, Schulz V *et al.* Non-obligatory role of prostaglandin D2 receptor subtype 1 in rosacea: laropiprant in comparison to a placebo did not alleviate the symptoms of erythematotelangiectatic rosacea. *J Clin Pharmacol* 2015; **55**:137–53.

32 Martel P, Jarratt M, Weiss J, Carlavan I. Lack of significant anti-inflammatory activity with clindamycin in the treatment of rosacea: results of 2 randomized, vehicle-controlled trials. *Cutis* 2017; **100**:53–8.

33 Mrowietz U, Kedem TH, Keynan R *et al.* A phase II, randomized, double-blind clinical study evaluating the safety, tolerability, and efficacy of a topical minocycline foam, FMX103, for the treatment of facial papulopustular rosacea. *Am J Clin Dermatol* 2018; **19**:427–36.

34 NCT00560703. Efficacy and safety of COL-101 for the treatment of blepharitis in patients with facial rosacea. Available at: https://clinicaltrials.gov/ct2/show/NCT00560703 (last accessed 13 September 2018).
35 NCT00617903. A 12-week exploratory, multicenter, double-blind, vehicle-controlled study to investigate the efficacy and safety of topical azelaic acid 15% foam twice daily in patients with papulopustular rosacea. Available at: https://clinicaltrials.gov/ct2/show/NCT00617903 (last accessed 13 September 2018).
36 NCT02147691. Finacea 15% and brimonidine 0.33% gel in the treatment of rosacea – a pilot study. Available at: https://clinicaltrials.gov/show/NCT02147691 (last accessed 13 September 2018).
37 Park SY, Kwon HH, Yoon J *et al.* Clinical and histologic effects of fractional microneedling radiofrequency treatment on rosacea. *Dermatol Surg* 2014; **42**:1362–9.
38 Raoufinejad K, Mansouri P, Rajabi M *et al.* Efficacy and safety of permethrin 5% topical gel vs. placebo for rosacea: a double-blind randomized controlled clinical trial. *J Eur Acad Dermatol Venereol* 2016; **30**:2105.
39 Sbidian E, Vicaut É, Chidiack H *et al.* A randomized-controlled trial of oral low-dose isotretinoin for difficult-to-treat papulopustular rosacea. *J Invest Dermatol* 2016; **136**:1124–9.
40 Seo HM, Kim JI, Kim HS *et al.* Prospective comparison of dual wavelength long-pulsed 755-nm alexandrite/1,064-nm neodymium:yttrium-aluminum-garnet laser versus 585-nm pulsed dye laser treatment for rosacea. *Ann Dermatol* 2016; **28**:607–14.
41 Stein Gold L, Kircik L, Fowler J *et al.* Long-term safety of ivermectin 1% cream vs azelaic acid 15% gel in treating inflammatory lesions of rosacea: results of two 40-week controlled, investigator-blinded trials. *J Drugs Dermatol* 2014; **13**:1380–6.
42 Stein Gold L, Papp K, Lynde C *et al.* Treatment of rosacea with concomitant use of topical ivermectin 1% cream and brimonidine 0.33% gel: a randomized, vehicle-controlled study. *J Drugs Dermatol* 2017; **16**:909–16.
43 van der Linden MMD, van Ratingen AR, van Rappard DC *et al.* DOMINO, doxycycline 40 mg vs. minocycline 100 mg in the treatment of rosacea: a randomized, single-blinded, noninferiority trial, comparing efficacy and safety. *Br J Dermatol* 2017; **176**:1465–74.
44 Zhang L, Wu ZX, Shen YN *et al.* The efficacy of hydroxychloroquine combined with 595 nm pulsed dye laser for acne rosacea. *J Clin Dermatol* 2017; **46**:413–17.
45 Zhong S, Sun N, Liu H *et al.* Topical tranexamic acid improves the permeability barrier in rosacea. *Dermatol Sin* 2015; **33**:112–17.
46 Berlin JM, Winkelman WJ. The role of long-term doxycycline 40 mg modified release in the prevention of disease relapse in moderate to severe rosacea. *J Am Acad Dermatol* 2015; **72** (Suppl. 1):AB11.
47 EUCTR2011-002058-30-DE. Effect of CD08100/02 3% gel versus placebo gel in subjects presenting with papulopustular rosacea over a 6-week treatment period. Available at: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011-002058-30-DE (last accessed 13 September 2018).
48 EUCTR2013-005083-26-DE. Effect of CD07805/47 gel in subjects presenting with flushing related to erythematotelangiectatic or papulopustular rosacea – effect of CD07805/47 gel in rosacea flushing. Available at: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2013-005083-26-DE (last accessed 13 September 2018).
49 Han G, Kang MC, Lee KS, Cho JW. Comparative split study on vascular lesions in Korean patients with conventional pulsed dye laser and IRIS laser. *J Dermatol* 2014; **41** (Suppl. 1):105.
50 Heitz A, Arnaud S, Merklen C *et al.* Oral azithromycin versus doxycyclin for the treatment of moderate to severe meibomian gland dysfunction (MGD): a randomized prospective non-inferiority study. *Invest Ophthalmol Vis Sci* 2014; **55**:1481.
51 Kuang AW, DuBois J, Attar M, Ahluwalia G. Clinical pharmacokinetics of oxymetazoline cream following topical facial administration for the treatment of erythema associated with rosacea. *J Drugs Dermatol* 2018; **17**:213–20.
52 NCT00697541. A phase II, single-center, two-way crossover relative systemic bioavailability study of Col-118 administered topically as a 0.18% facial gel and brimonidine ophthalmic solution 0.2% administered to the eye in subjects with moderate to severe erythematous rosacea. Available at: https://clinicaltrials.gov/ct2/show/NCT00697541 (last accessed 13 September 2018).
53 NCT01579084. Safety and tolerability of AGN-199201 in patients with erythema associated with rosacea. Available at: https://clinicaltrials.gov/show/NCT01579084 (last accessed 13 September 2018).
54 NCT01735201. AGN-199201 for the treatment of erythema with rosacea. Available at: https://clinicaltrials.gov/show/NCT01735201 (last accessed 13 September 2018).
55 NCT02300129. Effect of CD07805/47 gel in subjects presenting with flushing related to erythematotelangiectatic or papulopustular rosacea. Available at: https://clinicaltrials.gov/ct2/show/NCT02300129 (last accessed 13 September 2018).
56 NCT03035955. The effect of azelaic acid (Finacea gel 15%) on *Demodex folliculorum* counts in adult subjects with mild to moderate papulopustular rosacea. Available at: https://clinicaltrials.gov/ct2/show/NCT03035955 (last accessed 13 September 2018).
57 Waibel J, Wulkan A, Rudnick A. Prospective, randomized, controlled split-face study of the 532 nm KTP laser and 595 nm pulsed dye laser for the treatment of erythematotelangiectatic rosacea and papulopustular rosacea. *Lasers Surg Med* 2016; **48**:426.
58 Benkali K, Leoni M, Rony F *et al.* Comparative pharmacokinetics and bioavailability of brimonidine following ocular and dermal administration of brimonidine tartrate ophthalmic solution and gel in patients with moderate-to-severe facial erythema associated with rosacea. *Br J Dermatol* 2014; **171**:162–9.
59 Blom I, Hornmark AM. Topical treatment with sulfur 10 per cent for rosacea. *Acta Derm Venereol* 1984; **64**:358–9.
60 Buendia-Bordera G, Ciscar E. Skin barrier function assessment by *in vivo* confocal microscopy and other non-invasive optical measurements on patients suffering from rosacea to evaluate the efficacy of a post-laser serum. *Lasers Surg Med* 2013; **45** (Suppl. 25):43.
61 Draelos ZD, Green BA, Edison BL. An evaluation of a polyhydroxy acid skin care regimen in combination with azelaic acid 15% gel in rosacea patients. *J Cosmet Dermatol* 2006; **5**:23–9.
62 Draelos Z, Erthel K, Schnicker M *et al.* Facial foundation with niacinamide and N-acetylglucosamine improves skin condition in women with sensitive skin. *J Am Acad Dermatol* 2009; **60** (Suppl. 1):AB82.
63 Draelos Z, Hornby S, Walters RM, Appa Y. Hydrophobically modified polymers can minimize skin irritation potential caused by surfactant-based cleansers. *J Cosmet Dermatol* 2013; **12**:314–21.
64 Ertl GA, Levine N, Kligman AM. A comparison of the efficacy of topical tretinoin and low-dose oral isotretinoin in rosacea. *Arch Dermatol* 1994; **130**:319–24.

65 Espagne E, Guillaume JC, Archimbaud A *et al.* Double-blind study versus excipient of 0.75% metronidazole gel in the treatment of rosacea. *Ann Dermatol Venereol* 1993; **120**:129–33.

66 Fabi S, Peterson J, Goldman M. Combination 15% azelaic acid gel and intense pulse light therapy for mild to moderate rosacea. *Lasers Surg Med* 2011; **43** (Suppl. 23):968–9.

67 Guillet B, Rostain E, Powell F *et al.* Metronidazole 0.75% gel and lotion are both effective in the treatment of rosacea. *J Eur Acad Dermatol Venereol* 1999; **12** (Suppl.):S145.

68 Huang EY, Di Nardo A, Preson NJ *et al.* Multicenter, randomized, double-blind, placebo-controlled evaluation of rosacea related inflammatory biomarkers in papulopustular rosacea adults treated with doxycycline 40 mg modified release. *J Am Acad Dermatol* 2014; **70** (Suppl. 1):AB9.

69 Jorizzo JL, Lebwohl M, Tobey RE. The efficacy of metronidazole 1% cream once daily compared with metronidazole 1% cream twice daily and their vehicles in rosacea: a double blind clinical trial. *J Am Acad Dermatol* 1998; **39**:502–4.

70 Lupin M. Evaluation of the safety and effectiveness of microfocused ultrasound with visualization (MFU-V) for the treatment of erythematotelangiectatic rosacea. *J Am Acad Dermatol* 2014; **70** (Suppl. 1):AB43.

71 NCT00249782. A phase II, randomized, partial-blind, parallel-group, active- and vehicle-controlled, multicenter study of the safety and efficacy of ACZONE™ (dapsone) gel, 5% in subjects with papulopustular rosacea. Available at: https://clinicaltrials.gov/ct/show/NCT00249782 (last accessed 19 July 2014).

72 Rehmus W, Kim J. A double-blind, placebo-controlled study of a natural anti-inflammatory for treatment of rosacea. *J Am Acad Dermatol* 2006; **54** (Suppl.):AB64.

73 Thiboutot D. Efficacy and safety of subantimicrobial-dose doxycycline for the treatment of rosacea. *J Am Acad Dermatol* 2005; **52** (Suppl. 1):17.

74 Utaş S, Ünver Ü. Treatment of rosacea with ketoconazole. *J Eur Acad Dermatol Venereol* 1997; **8**:69–70.

75 Van Landuyt H, Joubert-Lequain I, Humbert P *et al.* Treatment of rosacea. Clonidine (0.075 mg per day) versus placebo (initial results). *Ann Dermatol Venereol* 1997; **124**:729.

76 Wilkin JK. Effect of nadolol on flushing reactions in rosacea. *J Am Acad Dermatol* 1989; **20**:202–5.

77 Wilkin JK, De Witt S. Treatment of rosacea: topical clindamycin versus oral tetracycline. *Int J Dermatol* 1993; **32**:65–7.

78 Wittpenn JR, Schechter B. Efficacy of cyclosporine a for the treatment of ocular rosacea. *Invest Ophthalmol Vis Sci* 2005; **46**:E-Abstract 2846.

79 Yoo J, Marmur E, Frankel AL *et al.* Combination therapy for the treatment of erythematotelangiectatic rosacea. *Lasers Surg Med* 2011; **43** (S23):918.

80 Akhyani M, Ehsani AH, Ghiasi M *et al.* Comparison of efficacy of azithromycin vs. doxycycline in the treatment of rosacea: a randomized open clinical trial. *Int J Dermatol* 2008; **47**:284–8.

81 Bamford JT, Tilden RL, Blankush JL *et al.* Effect of treatment of *Helicobacter pylori* infection on rosacea. *Arch Dermatol* 1999; **135**:659–63.

82 Barnhorst DA, Foster JA, Chern KC *et al.* The efficacy of topical metronidazole in the treatment of ocular rosacea. *Ophthalmology* 1996; **103**:1880–3.

83 Beutner K, Calvarese B. A multi-center, investigator-blind clinical trial to assess the safety and efficacy of metronidazole gel 1% as compared to metronidazole gel vehicle and metronidazole cream 1% in the treatment of rosacea. *J Am Acad Dermatol* 2005; **52** (Suppl. 3):P10.

84 Bitar A, Bourgouin J, Doré N *et al.* A double-blind randomised study of metronidazole (Flagyl) 1% cream in the treatment of acne rosacea, a placebo controlled study. *Drug Invest* 1990; **2**:242–8.

85 Bjerke JR, Nyfors A, Austad J *et al.* Metronidazole (Elyzol) 1% cream vs. placebo cream in the treatment of rosacea. *Clin Trials J* 1989; **26**:187–94.

86 Bjerke R, Fyrand O, Graupe K. Double-blind comparison of azelaic acid 20% cream and its vehicle in treatment of papulo-pustular rosacea. *Acta Derm Venereol* 1999; **79**:456–9.

87 Bleicher PA, Charles JH, Sober AJ. Topical metronidazole therapy for rosacea. *Arch Dermatol* 1987; **123**:609–14.

88 Breneman DL, Stewart D, Hevia O *et al.* A double-blind, multicenter clinical trial comparing efficacy of once-daily metronidazole 1 percent cream to vehicle in patients with rosacea. *Cutis* 1998; **61**:44–7.

89 Breneman D, Savin R, VandePol C *et al.* Double-blind, randomized, vehicle-controlled clinical trial of once-daily benzoyl peroxide/clindamycin topical gel in the treatment of moderate to severe rosacea. *Int J Dermatol* 2004; **43**:381–7.

90 Carmichael AJ, Marks R, Graupe KA *et al.* Topical azelaic acid in the treatment of rosacea. *J Dermatol Treat* 1993; **4** (Suppl. 1):S19–22.

91 Dahl MV, Katz HI, Krueger GG *et al.* Topical metronidazole maintains remissions of rosacea. *Arch Dermatol* 1998; **134**:679–83.

92 Dahl MV, Jarratt MJ, Kaplan D *et al.* Once-daily topical metronidazole cream formulations in the treatment of papules and pustules of rosacea. *J Am Acad Dermatol* 2001; **45**:723–30.

93 Del Rosso JQ, Webster GF, Jackson M *et al.* Two randomized phase III clinical trials evaluating anti-inflammatory dose doxycycline (40-mg doxycycline, USP capsules) administered once daily for treatment of rosacea. *J Am Acad of Dermatol* 2007; **56**:791–802.

94 Del Rosso JQ, Schlessinger J, Werschler P. Comparison of anti-inflammatory dose doxycycline versus doxycycline 100 mg in the treatment of rosacea. *J Drugs Dermatol* 2008; **7**:573–6.

95 Draelos ZD, Fuller BB. Efficacy of 1% 4-ethoxybenzaldehyde in reducing facial erythema. *Dermatol Surg* 2005; **31**:881–5.

96 Dreno B, Dubertret L, Naeyaert JM *et al.* Comparison of the clinical efficacy and safety of metronidazole 0.75% cream with metronidazole 0.75% gel in the treatment of rosacea. *J Eur Acad Dermatol Venereol* 1998; **11** (Suppl. 2):S272–3.

97 Elewski BE, Fleisher AB, Pariser DM. A comparison of 15% azelaic acid gel and 0.75% metronidazole gel in the topical treatment of papulopustular rosacea: results of a randomized trial. *Arch Dermatol* 2003; **139**:1444–50.

98 Fowler JF Jr. Combined effect of anti-inflammatory dose doxycycline (40-mg doxycycline, usp monohydrate controlled-release capsules) and metronidazole topical gel 1% in the treatment of rosacea. *J Drugs Dermatol* 2007; **6**:641–5.

99 Grosshans E, Michel C, Arcade B *et al.* Rilmenidine in rosacea: a double blind study versus placebo. *Ann Dermatol Venereol* 1997; **124**:687–91.

100 Karsai S, Roos S, Raulin C. Treatment of facial telangiectasia using a dual-wavelength laser system (595 and 1,064 nm): a randomized controlled trial with blinded response evaluation. *Dermatol Surg* 2008; **34**:702–8.

101 Koca R, Altinyazar HC, Ankarali H *et al.* A comparison of metronidazole 1% cream and pimecrolimus 1% cream in the treatment of patients with papulopustular rosacea: a randomized open-label clinical trial. *Clin Exp Dermatol* 2010; **35**:251–6.

102 Koch R, Wilbrand G. Dark sulfonated shale oil versus placebo in the systemic treatment of rosacea. *J Eur Acad Dermatol Venerol* 1999; **12** (Suppl. 32):S143–4.

103 Koçak M, Yagli S, Vahapoglu G *et al.* Permethrin 5% cream versus metronidazole 0.75% gel for the treatment of papulopustular rosacea. *Dermatology* 2002; **205**:265–70.

104 Lebwohl MG, Medansky RS, Russo CL, Plott RT. The comparative efficacy of sodium sulfacetamide 10%/sulfur 5% (Sulfacet-R)

lotion and metronidazole 0.75% (Metrogel) in the treatment of rosacea. *J Geriatr Dermatol* 1995; **3**:183–5.
105 Maddin S. A comparison of topical azelaic acid 20% cream and topical metronidazole 0.75% cream in the treatment of patients with papulopustular rosacea. *J Am Acad Dermatol* 1999; **40**:961–5.
106 Marks R, Ellis J. Comparative effectiveness of tetracycline and ampicillin in rosacea: a controlled trial. *Lancet* 1971; **2**:1049–52.
107 Monk BE, Logan RA, Cook J *et al.* Topical metronidazole in the treatment of rosacea. *J Dermatol Treat* 1991; **2**:91–3.
108 Montes LF, Cordero AA, Kriner J *et al.* Topical treatment of acne rosacea with benzoyl peroxide acetone gel. *Cutis* 1983; **32**:185–90.
109 Mostafa FF, El Harras MA, Gomaa SM *et al.* Comparative study of some treatment modalities of rosacea. *J Eur Acad Dermatol Venereol* 2009; **23**:22–8.
110 Neuhaus IM, Zane LT, Tope WD. Comparative efficacy of nonpurpuragenic pulsed dye laser and intense pulsed light for erythematotelangiectatic rosacea. *Dermatol Surg* 2009; **35**:920–8.
111 Nielsen PG. Treatment of rosacea with 1% metronidazole cream. *A double-blind study*. *Br J Dermatol* 1983; **108**:327–32.
112 Nielsen PG. A double-blind study of 1% metronidazole cream versus systemic oxytetracycline therapy for rosacea. *Br J Dermatol* 1983; **109**:63–5.
113 Pye RJ, Burton JL. Treatment of rosacea by metronidazole. *Lancet* 1976; **1**:1211–12.
114 Rigopoulos D, Kalogeromitros D, Gregoriou S *et al.* Randomized placebo-controlled trial of a flavonoid-rich plant extract-based cream in the treatment of rosacea. *J Eur Acad Dermatol Venereol* 2005; **19**:564–8.
115 Saihan EM, Burton JL. A double-blind trial of metronidazole versus oxytetracycline therapy for rosacea. *Br J Dermatol* 1980; **102**:443–5.
116 Sanchez J, Somolinos AL, Almodóvar PI *et al.* A randomized, double-blind, placebo-controlled trial of the combined effect of doxycycline hyclate 20-mg tablets and metronidazole 0.75% topical lotion in the treatment of rosacea. *J Am Acad Dermatol* 2005; **53**:791–7.
117 Sauder DN, Miller R, Gratton D *et al.* The treatment of rosacea: the safety and efficacy of sodium sulfacetamide 10% and sulfur 5% lotion (Novacet) is demonstrated in a double-blind study. *J Dermatol Treat* 1997; **8**:79–85.
118 Schachter D, Schachter RK, Long B *et al.* Comparison of metronidazole 1% cream versus oral tetracycline in patients with rosacea. *Drug Invest* 1991; **3**:220–4.
119 Schechter BA, Katz RS, Friedman LS. Efficacy of topical cyclosporine for the treatment of ocular rosacea. *Adv Ther* 2009; **26**:651–9.
120 Sharquie KE, Najim RA, Al-Salman HN. Oral zinc sulfate in the treatment of rosacea: a double-blind, placebo-controlled study. *Int J Dermatol* 2006; **45**:857–61.
121 Sneddon IB. A clinical trial of tetracycline in rosacea. *Br J Dermatol* 1966; **78**:649–52.
122 Tan JKL, Girard C, Krol A *et al.* Randomized placebo-controlled trial of metronidazole 1% cream with sunscreen SPF 15 in treatment of rosacea. *J Cutan Med Surg* 2002; **6**:529–34.
123 Thiboutot D, Thieroff-Ekerdt R, Graupe K. Efficacy and safety of azelaic acid (15%) gel as a new treatment for papulopustular rosacea: results from 2 vehicle-controlled, randomized phase III studies. *J Am Acad Dermatol* 2003; **48**:836–45.
124 Thiboutot DM, Fleisher AB, Del Rosso JQ *et al.* Azelaic acid 15% gel once daily versus twice daily in papulopustular rosacea. *J Drugs Dermatol* 2008; **7**:541–6.
125 Thiboutot DM, Fleischer AB, Del Rosso JQ *et al.* A multicenter study of topical azelaic acid 15% gel in combination with oral doxycycline as initial therapy and azelaic acid 15% gel as maintenance therapy. *J Drugs Dermatol* 2009; **8**:639–48.
126 Torok HM, Webster G, Dunlap FE *et al.* Combination sodium sulfacetamide 10% and sulfur 5% cream with sunscreens versus metronidazole 0.75% cream for rosacea. *Cutis* 2005; **75**:357–63.
127 Veien NK, Christiansen JV, Hjorth N *et al.* Topical metronidazole in the treatment of rosacea. *Cutis* 1986; **38**:209–10.
128 Verea Hernando M, Margusino Framiñán L, Seco Vilariño C *et al.* Comparative study of topical erythromycin and topical metronidazole in the treatment of rosacea. *Farm Clin* 1992; **9**:472–9.
129 Weissenbacher S, Merkl J, Hildebrandt B *et al.* Pimecrolimus cream 1% for papulopustular rosacea: a randomized vehicle-controlled double-blind trial. *Br J Dermatol* 2007; **156**:728–32.
130 Wolf JE Jr, Kerrouche N, Arsonnaud S. Efficacy and safety of once-daily metronidazole 1% gel compared with twice-daily azelaic acid 15% gel in the treatment of rosacea. *Cutis* 2006; **77** (Suppl. 4):3–11.
131 Alam M, Voravutinon N, Warycha M *et al.* Comparative effectiveness of nonpurpuragenic 595-nm pulsed dye laser and microsecond 1064-nm neodymium:yttrium-aluminum-garnet laser for treatment of diffuse facial erythema: a double-blind randomized controlled trial. *J Am Acad Dermatol* 2013; **69**:438–43.
132 Bamford JT, Gessert CE, Haller IV *et al.* Randomized, double-blind trial of 220 mg zinc sulfate twice daily in the treatment of rosacea. *Int J Dermatol* 2012; **51**:459–62.
133 Berardesca E, Iorizzo M, Abril E *et al.* Clinical and instrumental assessment of the effects of a new product based on hydroxypropyl chitosan and potassium azeloyl diglycinate in the management of rosacea. *J Cosmet Dermatol* 2012; **11**:37–41.
134 Bribeche MR, Fedotov VP, Gladichev VV *et al.* Clinical and experimental assessment of the effects of a new topical treatment with praziquantel in the management of rosacea. *Int J Dermatol* 2015; **54**:481–7.
135 Chang AL, Alora-Palli M, Lima XT *et al.* A randomized, double-blind, placebo-controlled, pilot study to assess the efficacy and safety of clindamycin 1.2% and tretinoin 0.025% combination gel for the treatment of acne rosacea over 12 weeks. *J Drugs Dermatol* 2012; **11**:333–9.
136 Del Rosso JQ, Bruce S, Jarratt M *et al.* Efficacy of topical azelaic acid (AzA) gel 15% plus oral doxycycline 40 mg versus metronidazole gel 1% plus oral doxycycline 40 mg in mild-to-moderate papulopustular rosacea. *J Drugs Dermatol* 2010; **9**:607–13.
137 Draelos ZD, Elewski B, Staedtler G, Havlickova B. Azelaic acid foam 15% in the treatment of papulopustular rosacea: a randomized, double-blind, vehicle-controlled study. *Cutis* 2013; **92**:306–17.
138 Fowler J, Jarratt M, Moore A *et al.* Once-daily topical brimonidine tartrate gel 0.5% is a novel treatment for moderate to severe facial erythema of rosacea: results of two multicentre, randomized and vehicle-controlled studies. *Br J Dermatol* 2012; **166**:633–41.
139 Fowler J Jr, Jackson M, Moore A *et al.* Efficacy and safety of once-daily topical brimonidine tartrate gel 0.5% for the treatment of moderate to severe facial erythema of rosacea: results of two randomized, double-blind, and vehicle-controlled pivotal studies. *J Drugs Dermatol* 2013; **12**:650–6.
140 Gollnick H, Blume-Peytavi U, Szabó EL *et al.* Systemic isotretinoin in the treatment of rosacea - doxycycline - and placebo-controlled, randomized clinical study. *J Deutsch Dermatol Ges* 2010; **8**:505–15.
141 Huang YE, Li XL, Li TJ. [Clinical research of topical tacrolimus ointment combined with 585 nm pulsed dye laser in the treatment of rosacea]. *J Clinical Dermatol* 2012; **41**:308–9 (in Chinese).
142 Jackson JM, Kircik LH, Lorenz DJ. Efficacy of extended-release 45 mg oral minocycline and extended-release 45 mg oral minocycline plus 15% azelaic acid in the treatment of acne rosacea. *J Drugs Dermatol* 2013; **12**:292–8.

143 Kendall J, Winkelman W. A comparison of 3 assessments in the treatment of rosacea in the context of a comparative effectiveness study. *Value Health* 2014; **17**:A181–2.
144 Kim TG, Roh HJ, Cho SB *et al.* Enhancing effect of pretreatment with topical niacin in the treatment of rosacea-associated erythema by 585-nm pulsed dye laser in Koreans: a randomized, prospective, split-face trial. *Br J Dermatol* 2011; **38**:510–13.
145 Leyden JJ. Efficacy of a novel rosacea treatment system: an investigator-blind, randomized, parallel-group study. *J Drugs Dermatol* 2011; **10**:1179–85.
146 Leyden JJ. Randomized, phase 2, dose-ranging study in the treatment of rosacea with encapsulated benzoyl peroxide gel. *J Drugs Dermatol* 2014; **13**:685–8.
147 Luger T, Peukert N, Rother M. A multicentre, randomized, placebo-controlled trial establishing the treatment effect of TDT 068, a topical formulation containing drug-free ultra-deformable phospholipid vesicles, on the primary features of erythematotelangiectatic rosacea. *J Eur Acad Dermatol Venereol* 2015; **29**:283–90.
148 NCT01426269. Evaluation of relapse, efficacy and safety of long-term treatment with Oracea® capsules compared to placebo after an initial 12 week treatment regimen with Oracea® and MetroGel® 1% in adults with rosacea. Available at: https://clinicaltrials.gov/ct2/show/NCT01426269 (last accessed 21 July 2014).
149 NCT01449591. A proof of concept (PoC) study to evaluate the safety, tolerability, and efficacy of 12 week administration of BFH772 ointment in rosacea patients. Available at: https://clinicaltrials.gov/ct2/show/NCT01449591 (last accessed 19 July 2014).
150 Layton AM, Schaller M, Homey B *et al.* Brimonidine gel 0.33% rapidly improves patient-reported outcomes by controlling facial erythema of rosacea: a randomized, double-blind, vehicle-controlled study. *J Eur Acad Dermatol Venerol* 2015; **29**:2405–10.
151 Nymann P, Hedelund L, Haedersdal M. Long-pulsed dye laser vs. intense pulsed light for the treatment of facial telangiectasias: a randomized controlled trial. *J Eur Acad Dermatol Venereol* 2010; **24**:143–6.
152 Rodríguez Acar M, Medina Hernández E. A comparative, double-blind study about efficacy and safety of crotamiton vs benzyl benzoate in the treatment of rosacea with demodecidosis. *Dermatol Rev Mex* 2003; **47**:126–30.
153 Salem DA, El-Shazly A, Nabih N *et al.* Evaluation of the efficacy of oral ivermectin in comparison with ivermectin-metronidazole combined therapy in the treatment of ocular and skin lesions of *Demodex folliculorum*. *Int J Infect Dis* 2013; **17**:343–7.
154 Seité S, Benech F, Berdah S *et al.* Management of rosacea-prone skin: evaluation of a skincare product containing Ambophenol, Neurosensine, and La Roche-Posay Thermal spring water as monotherapy or adjunctive therapy. *J Drugs Dermatol* 2013; **12**:920–4.
155 Stein L, Kircik L, Fowler J *et al.* Efficacy and safety of ivermectin 1% cream in treatment of papulopustular rosacea: results of two randomized, double-blind, vehicle-controlled pivotal studies. *J Drugs Dermatol* 2014; **13**:316–23.
156 Taieb A, Ortonne JP, Ruzicka T *et al.* Superiority of ivermectin 1% cream over metronidazole 0.75% cream in treating inflammatory lesions of rosacea: a randomized, investigator-blinded trial. *Br J Dermatol* 2015; **172**:1103–10.
157 Tirnaksiz F, Kayiş A, Çelebi N *et al.* Preparation and evaluation of topical microemulsion system containing metronidazole for remission in rosacea. *Chem Pharm Bull (Tokyo)* 2012; **60**:583–92 .
158 Two AM, Hata TR, Nakatsuji T *et al.* Reduction in serine protease activity correlates with improved rosacea severity in a small, randomized pilot study of a topical serine protease inhibitor. *J Invest Dermatol* 2014; **134**:1143–5.
159 Basra MK, Fenech R, Gatt RM *et al.* The Dermatology Life Quality Index 1994–2007: a comprehensive review of validation data and clinical results. *Br J Dermatol* 2008; **159**:997–1035.
160 Basra MK, Salek MS, Camilleri L *et al.* Determining the minimal important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. *Br J Dermatol* 2015; **230**:27–33.
161 van Zuuren EJ, Fedorowicz Z, Carter B *et al.* Interventions for rosacea. *Cochrane Database Syst Rev* 2015; **4**:CD003262.
162 Asai Y, Tan J, Baibergenova A *et al.* Canadian clinical practice guidelines for rosacea. *J Cutan Med Surg* 2016; **20**:432–45.
163 Anzengruber F, Czernielewski J, Conrad C *et al.* Swiss S1 guideline for the treatment of rosacea. *J Eur Acad Dermatol* 2017; **31**:1775–91.
164 Deeks ED. Ivermectin: a review in rosacea. *Am J Clin Dermatol* 2015; **16**:447–52.
165 Ebbelaar CCF, Venema AW, van Dijk MR. Topical ivermectin in the treatment of papulopustular rosacea: a systematic review of evidence and clinical guideline recommendations. *Dermatol Ther* 2018; **8**:379–87.
166 Siddiqui K, Stein Gold L, Gill J. The efficacy, safety, and tolerability of ivermectin compared with current topical treatments for the inflammatory lesions of rosacea: a network meta-analysis. *SpringerPlus* 2016; **5**:1151.
167 van Zuuren EJ, Kramer S, Carter B *et al.* Interventions for rosacea. *Cochrane Database Syst Rev* 2011; **3**:CD003262.

Appendix 1

Conflicts of interest

E.J.v.Z. serves on the global ROSacea COnsensus panel (ROSCO) and received nonfinancial support and other support from Galderma in October 2016. J.T. has been an advisor, consultant, investigator and/or speaker for Allergan, Bayer, Cipher, Galderma and Valeant. J.T. was a co-author of the Canadian Rosacea Clinical Practice Guidelines and is the co-chair of ROSCO and serves on the expert panel of the National Rosacea Society. J.T. was an investigator in the following trials: Stein *et al.*,[155] Stein Gold *et al.*,[41] Stein Gold *et al.*[42] and Tan *et al.*[122] M.M.D.v.d.L. received nonfinancial support and other support from Galderma in October 2016, and received speaker fees from Janssen Cilag and AbbVie. Furthermore, M.M.D.v.d.L. was an investigator in the following trial: van der Linden MMD *et al.*[43]

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1. Full updated review.
Video S1. Author video.
Powerpoint S1. Journal Club Slide Set.