Rosacea: new concepts in classification and treatment

Zuuren, E.J. van; Arents, B.W.M.; Linden, M.M.D. van der; Vermeulen, S.; Fedorowicz, Z.; Tan, J.

American Journal of Clinical Dermatology (2021) 22:457–465
https://doi.org/10.1007/s40257-021-00595-7

LEADING ARTICLE

Rosacea: New Concepts in Classification and Treatment

Esther J. van Zuuren[1] · Bernd W. M. Arents[2] · Mireille M. D. van der Linden[3] · Sofieke Vermeulen[4] · Zbys Fedorowicz[5] · Jerry Tan[6]

Accepted: 18 February 2021 / Published online: 23 March 2021

Abstract
Rosacea is a chronic inflammatory dermatosis mainly affecting the cheeks, nose, chin, and forehead. Rosacea is characterized by recurrent episodes of flushing or transient erythema, persistent erythema, phymatous changes, papules, pustules, and telangiectasia. The eyes may also be involved. Due to rosacea affecting the face, it has a profound negative impact on quality of life, self-esteem, and well-being. In addition to general skin care, there are several approved treatment options available for addressing these features, both topical and systemic. For some features, intense pulse light, laser, and surgery are of value. Recent advances in fundamental scientific research have underscored the roles of the innate and adaptive immune systems as well as neurovascular dysregulation underlying the spectrum of clinical features of rosacea. Endogenous and exogenous stimuli may initiate and aggravate several pathways in patients with rosacea. This review covers the new phenotype-based diagnosis and classification system reflecting pathophysiology, and new and emerging treatment options and approaches. We address new topical and systemic formulations, as well as recent evidence on treatment combinations. In addition, ongoing studies investigating novel therapeutic interventions will be summarized.

1 Introduction

Rosacea is a chronic inflammatory disease predominantly affecting the centrofacial region (cheeks, chin, nose, and forehead) and the eyes [1–4]. Rosacea is characterized by recurrent episodes of flushing, persistent erythema, inflammatory papules/pustules, and telangiectasia. Phymatous changes are infrequent, occurring primarily at the nose (rhinophyma) and more frequently in men [1, 5]. More than half of patients with rosacea have ocular features including dryness, foreign-body sensation, photophobia, conjunctivitis, blepharitis, and in rare cases, keratitis that may compromise eyesight [1]. Rosacea usually starts between 30 to 50 years of age, but can occur at any age [1, 3]. Prevalence rates across populations range from < 1 to 22%, but these percentages are likely to be influenced by differences in study design, methodology, population, geographical location, and cultural and social differences in perception of the disease [6, 7]. In a recent systematic review, the global prevalence of rosacea was estimated at 5.5% of the adult population. Furthermore, men and

Key Points

The updated phenotype-based diagnosis and classification system based on features enables accurate characterization of individual patients and the potential for optimizing outcomes by addressing features most bothersome to the patient.

Treatment optimization may be enabled by new evidence on treatment combinations and the upcoming availability of new topical/oral formulations of existing medications.

Various novel therapeutic interventions are being investigated, some based on the increased understanding of rosacea's pathophysiology.

✉ Esther J. van Zuuren
e.j.van_zuuren@lumc.nl

1 Department of Dermatology, Leiden University Medical Center, Leiden, The Netherlands

2 Skin Patients Netherlands, Nieuwerkerk a/d IJssel, The Netherlands

3 Department of Dermatology, Amsterdam University Center, Amsterdam, The Netherlands

4 Department of Dermatology, Reinier de Graaf Hospital, Delft, The Netherlands

5 Veritas Health Sciences Consultancy, Huntingdon, UK

6 Department of Medicine, Western University, Windsor Campus, Windsor, ON, Canada

women were found to be equally affected [8], in contrast to previous studies which found a greater prevalence in women [1, 3]. Additionally, rosacea is more frequently observed in populations with fair skin of Celtic and northern European descent [1]. However, in individuals with darker phototypes, rosacea is likely unrecognized and under-diagnosed as erythema and telangiectasia are more difficult to discern [4, 9]. Rosacea can lead to embarrassment, low self-esteem, anxiety, depression, and stigmatization. Furthermore, it has an adverse impact on quality of life, social and psychological well-being [1, 10, 11]. Recent studies have reported possible associations of rosacea with increased risk of cardiovascular, gastrointestinal, neurological, auto-immune, and psychiatric disorders along with an increased risk of cancer. Whether these associations have a causal relationship requires further evaluation [12–14].

In addition to identification and avoidance of patient-specific triggers, self-care advice, and general skin care measures, there are active treatment options available for addressing rosacea features [1, 4, 5]. Approved treatments for erythema include topical brimonidine and oxymetazoline; and for papules/pustules topical ivermectin, metronidazole, azelaic acid, and oral doxycycline 40 mg modified release. Laser and light-based therapies can be used for telangiectasia, erythema, and phyma. The latter may also require surgical correction [1, 4, 5].

This paper reviews the updated knowledge of pathophysiology, the new phenotype-based diagnosis and classification of rosacea (Table 1), recent evidence on new combinations of treatments, and new and emerging treatment options (Table 2).

2 Pathophysiology

Current inflammatory pathways relevant to rosacea pathogenesis include dysregulation of immune (innate, adaptive, inflammasome) and neurocutaneous mechanisms [15, 16]. Genetic susceptibility with modified immune reactivity is suggested by the association of rosacea with single nucleotide polymorphisms in genes associated with the major histocompatibility complex [17].

Innate and adaptive immune activation may be triggered by microbes including Demodex species and various bacteria including *Bacillus oleronius* and *Staphylococcus epidermidis* [18]. Innate immune activation leads to upregulation of keratinocyte-derived toll-like receptor 2 (TLR2) and proteinase-activated receptor 2 (PAR2). These promote expression of the antimicrobial peptide cathelicidin, which is subsequently activated to bioactive LL-37 by kallikrein 5 (KLK-5) protease, leading to erythema and angiogenesis [19]. TLR2 facilitates activation of the NLRP3 inflammasome leading to pustule formation, pain, and vascular responsivity via interleukin-1β and tumor necrosis factor-alpha (TNF-α); and prostaglandin E2 release. Furthermore, TLR2 can elicit erythema, telangiectasia, and inflammation via expression of cytokines, chemokines, proteases, and angiogenic factors. PAR2 activation leads to inflammation, pruritus, and pain combined with recruitment of T lymphocytes and neutrophils, degranulation of mast cells, and further release of inflammatory chemokines, cytokines, and prostaglandins [15]. Adaptive immune system activation, demonstrated by presence of T helper type I (TH1) and T helper 17 (TH17) lymphocytes with their relevant immune mediators, results in increased inflammation and further immune activation [20, 21].

Neurocutaneous mechanisms in rosacea—reflecting reactivity to temperature change, exercise, UV, spicy food, and alcohol—may be mediated through transient receptor potential (TRP) ankyrin and vanilloid subfamilies. Specific subfamily receptors may respond to different external triggers leading to release of vasoactive neuro peptides (substance P, pituitary adenylate cyclase-activating peptide, calcitonin gene-related peptide). Sensory nerves also express TLR2 and PAR2 and can perpetuate activation of inflammatory mechanisms [22].

3 Updated Diagnosis and Classification System of Rosacea

In 2002, the American National Rosacea Society provided a provisional diagnosis and classification system to facilitate communication by using standard criteria between

Table 1 Diagnostic, major, and minor features of rosacea [2]

Diagnostic features	Major features	Minor features
Persistent centrofacial erythema with periodic intensification by potential trigger factors	Flushing/transient centrofacial erythema	Burning sensation of the skin
Phymatous changes	Inflammatory papules and pustules	Stinging sensation of the skin
	Telangiectasia (excluding alar involvement)	Edema
	Ocular manifestations:	Dry sensation of the skin
	Lid margin telangiectasia	
	Blepharitis	
	Keratitis/conjunctivitis/sclerokeratitis	

Table 2 Agents under development or recently approved, and new and emerging indications of existing drugs for treating rosacea

Agent	Manufacturer	Route of administration	Patients enrolled	Phase, status and reference
B244 spray	AOBiome LLC	Topical	140	Phase II, completed [50]
DMT210 5% gel	Dermata Therapeutics	Topical	104	Phase II, completed [58]
Encapsulated benzoyl peroxide cream (1% and 5%); brand name: Epsolay® (5%)	Sol-Gel technologies, Ltd.	Topical	733	Phase III, completed [41–46], under FDA review, and FDA assigned Prescription Drug User Fee Act for April 2021 [47]
Erenumab 140 mg 4-weekly; brand name Aimovig®	Novartis Pharmaceuticals Corporation	Subcutaneous	30	Phase II, recruiting [49]
Hydroxychloroquine 200 mg twice daily	Various manufacturers	Oral	6	Pilot study [59]
			66	Pilot study [60]
Minocycline				
Minocycline extended release capsules (DFD-29 20 and 40 mg)	Dr Reddy's Laboratories Ltd	Oral	205	Phase II, completed [40]
Minocycline foam (FMX103 1.5% and 3%); brand name: Zilxi™ (1.5%)	VYNE Therapeutics Inc.	Topical	1522	Phase III, completed, FDA approved [37, 38]
Minocycline gel 1% and 3%	Hovione Scientia, Ltd	Topical	270	Phase IIb, completed [39]
Omiganan gel	Maruho Co., Ltd	Topical	240	Phase II, completed [53]
			307	Phase III, completed [51]
			463	Phase III, completed [54]
			263	Phase III, completed [52]
Rifaximin; brand name Xifaxan®	Alfasigma S.p.A	Oral	236	Phase II, completed [57]
Secukinumab 300 mg weekly for 5 weeks then monthly; brand name Cosentyx®	Novartis Pharmaceuticals Corporation	Subcutaneous	24	Phase Ib, completed [48]

clinicians, researchers, patients, and health and insurance organizations [23]. In this schema, any of the following primary features in a central distribution on the face was diagnostic for rosacea: flushing (transient erythema), non-transient erythema, papules and pustules, and telangiectasia. Secondary features, which may be present with primary features or appear independently, included burning or stinging sensation, plaque, dry appearance, edema, ocular manifestations, peripheral location, and phymatous changes [23]. Furthermore, they proposed four presentations called subtypes (erythematotelangiectatic, papulopustular, phymatous, ocular) and one variant (granulomatous). This system has subsequently been widely used for diagnosis, classification, and treatment of rosacea by clinicians and researchers and in the scientific literature [2, 3, 24]. With increased clinical use, shortcomings of this system in diagnosis and classification were increasingly recognized [1–3, 5, 24]. Diagnostic shortcomings were inclusion of features with low predictive value (flushing, papules/pustules, telangiectasia) and exclusion of phyma, of high predictive value. In subtyping, shortcomings included conflation of multiple features into discrete categories that did not accurately represent the presentation of rosacea patients and within which it was impossible to evaluate the relative prevalence of each feature. This fostered a degree of confusion in epidemiological and clinical trial research due to the inability to accurately evaluate key features of interest [1–3, 5, 24]. Consequently, a schema established on patient features that encompassed the diversity of clinical presentations was proposed by the global ROSacea COnsensus (ROSCO) panel in 2017. This phenotype approach was based on an "individual's observable characteristics that can be influenced by genetic or environmental factors" [2]. The ROSCO panel represented an international rosacea expert group of dermatologists and ophthalmologists from Asia, Africa, Europe, North America, and South America to ensure global representation [2]. In this paradigm, subsequently endorsed by the National Rosacea Society [3], two features were independently diagnostic for rosacea [2]. In their absence, the presence of two or more major features can establish the diagnosis. Furthermore, minor features might also present with diagnostic and/or major features (Table 1). The next step was to align the

management strategies with the phenotype approach to enable optimization of patient outcomes and improve general well-being by targeting those features most bothersome to the patient [1, 4, 25].

4 Combination of Treatments

Although combination therapy is common practice among dermatologists and widely recommended, there is only limited evidence supporting its efficacy [1, 4, 26].

4.1 Combination of Topical Metronidazole with Oral Doxycycline 40 mg Modified Release (DMR)

In a randomized, double-blind study with a small sample size ($n = 72$), DMR was combined with topical metronidazole 1% gel once daily in patients with mild to moderate rosacea and compared with topical metronidazole 1% gel once daily [27]. The combined treatment significantly reduced inflammatory lesions when compared with metronidazole 1% gel monotherapy as early as week 4 and this difference remained significant to week 12 (13.86 lesions vs 8.47; $p = 0.002$). Improvements in both IGA and erythema at week 12 were also significantly greater in the combination group indicating that combined treatments can be effective for more than one feature.

Another randomized, double-blind study in 40 rosacea participants compared twice-daily doxycycline 20 mg plus metronidazole 0.75% gel with placebo plus metronidazole 0.75% over 16 weeks [28]. These results were similar to the study summarized above.

4.2 Combination of Topical Brimonidine and Topical Ivermectin

Topical brimonidine (addressing erythema) and topical ivermectin (addressing inflammatory papules/pustules) are registered for treating rosacea. A randomized, double-blind, vehicle-controlled trial of 190 participants with moderate to severe rosacea (investigator global assessment (IGA) score of 3–4 on a scale of 0–4, higher being worse; having both erythema and inflammatory lesions) evaluated the combination of brimonidine 0.33% gel in the morning and ivermectin 1% cream in the evening [29]. The first group ($n = 49$) received combination treatment for 12 weeks; the second ($n = 46$) had brimonidine vehicle in the morning and ivermectin 1% cream in the evening for the first 4 weeks, followed by brimonidine 0.33% gel in the morning, and ivermectin 1% cream in the evening for 8 weeks; and the third group ($n = 95$) had brimonidine vehicle in the morning and ivermectin vehicle in the evening.

More participants in the first group (total active) achieved IGA success (clear [0]/almost clear [1]; overall assessment including background erythema and inflammatory lesions) compared with the third or vehicle group (55.8% vs 36.8%; $p = 0.007$). The benefit of brimonidine from the outset with ivermectin (first group) was apparent by week 4 with IGA success in 22.4%; group 2 (the first 4 weeks without brimonidine, only use of ivermectin) in 13%, and vehicle-only group in 9.5%. The reductions in erythema and inflammatory lesions and the self-reported improvement supported the add-on effect of brimonidine gel to ivermectin cream.

4.3 Combination of Topical Ivermectin with Oral Doxycycline 40 mg Modified Release

Topical ivermectin and DMR are registered for treating rosacea, and both address inflammation. One recent phase IIIb/IV, randomized, investigator-blinded trial in 273 participants with severe rosacea (IGA 4) compared ivermectin 1% cream and DMR with ivermectin 1% cream combined with placebo [30]. After 12 weeks, both regimens resulted in lesion count reduction, but the combination was more effective (80.3% versus 73.6%, respectively; $p = 0.032$). Furthermore, combination treatment had a faster onset of action with a difference noted by week 4, and more participants achieved IGA 0 (11.9% vs 5.1%; $p = 0.043$) and 100% lesion reduction (17.8% vs 7.2%; $p = 0.006$). Both treatment groups also experienced improvements in erythema, stinging, burning, flushing, and ocular signs and symptoms. Few adverse events were reported in both groups.

5 Minocycline

Minocycline is a second-generation, semi-synthetic derivative of tetracycline with both bacteriostatic and anti-inflammatory effects. Minocycline is more lipophilic than the other tetracyclines. The anti-inflammatory effects of tetracyclines include inhibition of metalloproteinases, inhibition of bacterial products that induce inflammation, and inhibition of phospholipase A2. Furthermore, tetracyclines decrease nitric oxide (NO) and inducible nitric oxide synthase (iNOS) (which cause vasodilation) and suppress neutrophil migration and chemotaxis, granuloma formation, and pro-inflammatory cytokine release (such as TNFα, IL-1β and IL-6). Minocycline also has antioxidant capacity by decreasing free radical production and is a potent reactive oxygen species scavenger [1, 31–35]. Oral minocycline is used off-label in treatment of rosacea but evidence is limited, and there is a small risk of serious side effects with systemic use [32, 36].

5.1 Minocycline Foam

The United States Food and Drug Administration (FDA) approved topical minocycline foam 1.5% (FMX103) in May 2020. The foam has been available since October 2020 in the United States. A phase II, dose-ranging, randomized, double-blind trial evaluated the safety, tolerability, and efficacy of minocycline foam (FMX103) for moderate-to-severe papulopustular rosacea [37]. The study comprised 1.5% and 3% FMX103 and vehicle, involving 232 subjects over 12 weeks. Mean reduction in lesion counts from baseline to week 12 was 21.1 (from baseline mean 34.5) for the 1.5% group, 19.9 (from 34.1) for the 3% group and 7.8 (from 30.6) for vehicle. Reductions with both concentrations of FMX103 were significantly greater than for vehicle ($p < 0.001$). Proportions achieving at least a two-grade improvement in IGA were 41.8% for 1.5% FMX103, 33.3% for 3% FMX103, and 17.9% for vehicle ($p = 0.002$ and $p = 0.032$ pairwise comparisons to vehicle respectively). Both doses were safe and well tolerated [37].

Subsequently, two identical, phase III, randomized, double-blind, vehicle-controlled studies were conducted with 1.5% FMX103 ($n = 751$ and 771) [38]. Primary efficacy endpoints at week 12 were absolute change from baseline in inflammatory lesion counts, and proportion of subjects with treatment success defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a two-grade reduction. In study I, the reduction in inflammatory lesion counts in the 1.5% FMX103 group was 17.57 (baseline 28.5) versus 15.65 (baseline 29.0) in the vehicle group ($p = 0.0031$), and in study II, corresponding reductions were 18.54 (baseline 30.0) versus 14.88 (baseline 30.2) ($p < 0.0001$). In study I, 52.1% achieved treatment success with the FMX103 1.5% group compared with 43.0% on vehicle ($p = 0.0273$) and in study II, it was 49.1% versus 39.0% ($p = 0.0077$). There were no serious treatment-related adverse events. Most adverse events were mild to moderate, with upper respiratory tract infection being the most common overall, and pruritus being the most common cutaneous adverse event. Head-to-head studies are needed to establish the relative efficacy of topical minocycline in comparison with topical ivermectin, azelaic acid, and metronidazole.

5.2 Minocycline Gel

Still under investigation is minocycline gel. A phase IIb randomized, double-blind, vehicle-controlled trial evaluated the efficacy and safety of 1% and 3% minocycline gel in 270 participants over 12 weeks [39]. The primary efficacy endpoint was absolute change from baseline in inflammatory lesions at week 12. Secondary endpoints included proportions achieving IGA success for inflammatory lesions (achievement of 'clear' or 'almost clear' and a two-point reduction in score). Assessments of IGA for lesion severity and erythema (IGAe) were also included and data were collected at each visit regarding safety and tolerability. At 12 weeks, decrease in lesion counts was 12.6 (baseline 24.6) in the minocycline 1% group; 13.1 (baseline 25.1) in the minocycline 3% group, and 7.9 (baseline 24.3) with vehicle. Pairwise comparisons to vehicle were significant ($p = 0.015$ and $p = 0.0073$, respectively) and absolute differences in lesion reduction were four to five lesions compared with vehicle. IGA success was achieved in 39% in the minocycline 1% group, 46% in the minocycline 3% group, and 31% in the vehicle group. Only the difference between minocycline 3% and vehicle was statistically significant ($p = 0.038$). IGAe change showed no significant difference between groups. The number of treatment-related adverse events was low: 3% in the minocycline 1% group, 5% in the minocycline 5% group, and 1% in the vehicle group. The authors suggest further evaluation of minocycline gel, which shows comparable results to minocycline foam.

5.3 Oral Low-Dose Minocycline: DFD-29 Extended-Release Capsules

A multi-center, randomized, double-blind, controlled phase II study evaluated the efficacy of DFD-29 extended-release capsules in 205 patients with papulopustular rosacea [40]. Patients were randomized into four groups: DFD-29 40 mg, DFD-29 20 mg, doxycycline 40 mg, and placebo capsules, once daily for 16 weeks. Treatment success was defined as IGA 0 or 1 with at least a 2-grade reduction from baseline. After 16 weeks, treatment success was highest for DFD-29 40 mg (66%) followed by doxycycline 40 mg (33.3%), DFD-29 20 mg (31.9%) and placebo (11.5%). Furthermore, DFD-29 40 mg resulted in total inflammatory lesion count reduction of 19.2, DFD-29 20 mg of 12.6, doxycycline 40 mg of 10.5, and placebo of 7.3. Quality of life, measured with the RosaQol, improved most in the DFD-29 40-mg group. Common adverse events in all treatment groups were nasopharyngitis and diarrhea. Headache was reported most in the DFD-29 40-mg group (42.3%) compared with the other groups (29–37%). Further evaluation will be needed to confirm these promising results.

6 Encapsulated Benzoyl Peroxide Cream

Benzoyl peroxide is widely used in the treatment of acne in view of its antibacterial properties. Use in rosacea had not been investigated due to prior concern of skin irritation. Encapsulating benzoyl peroxide in silica microcapsules might mitigate irritation and studies were undertaken to assess its effect in rosacea [41].

A phase II, dose-ranging, randomized, double-blind, vehicle-controlled study with 90 rosacea subjects over 12 weeks demonstrated that 5% encapsulated benzoyl peroxide outperformed 1% benzoyl peroxide cream in achieving treatment success (two-grade improvement in IGA compared with baseline) [41]. Subsequently, two identical phase III randomized, double-blind, vehicle-controlled trials of micro-encapsulated benzoyl peroxide (E-BPO 5% cream) were conducted ($n = 361$ and 372) in moderate or severe papulopustular rosacea [42–44]. Subjects were randomized to either active or vehicle once daily for 12 weeks. Primary efficacy endpoints were proportion achieving IGA clear/almost clear (0/1) and absolute change in inflammatory lesion counts. In both trials, the E-BPO 5% cream groups achieved a greater proportion of IGA 0/1 compared with vehicle groups (43.5% versus 16.1% and 50.1% versus 25.9%, respectively). Absolute mean reduction in lesion counts from baseline were 17.4 versus 9.5, and 20.3 versus 13.3, respectively. Most frequently reported adverse events were application-site erythema and pain, mild to moderate in severity. Local tolerability (dryness, scaling, itching, burning/stinging) of E-BPO 5% cream was similar to vehicle. A 52-week, open-label trial for 547 subjects completing the two phase II trials was conducted to evaluate long-term safety and efficacy of E-BPO 5% cream daily [45, 46]. Upon attaining an IGA score of 0/1, treatment application was halted but resumed with loss of global success. An IGA score of 0/1 was achieved in 67.2% of the participants. For those who had an IGA of 0/1 at the beginning of this study, mean time to restart treatment was 125 days (mean number of retreatments 1.15). In contrast, those who had an IGA of 1 'almost clear' had a mean time to retreatment of 93 days (mean number of retreatments 1.7) ($p < 0.05$ for both comparisons). While 10 subjects experienced serious adverse events, none were considered related to study treatment. The FDA accepted for review the new drug application of 5% encapsulated benzoyl peroxide cream for rosacea in September 2020. A target action date of April 2021 has been set for the Prescription Drug User Fee Act [47].

7 Biologics

7.1 Secukinumab

Secukinumab, a human monoclonal antibody registered for treating psoriasis, binds to IL-17A which is involved in the inflammatory process. For papulopustular rosacea, an open-label, rater-blinded, investigator-initiated trial with secukinumab 300 mg weekly for 5 weeks, and then monthly for 2 months was completed in 2019 [48]. Of 24 patients recruited, 17 completed. Significant reductions at 16 weeks were observed in both papules (median reduction of 5 lesions; $p = 0.01$) and global severity score (by 0.3 points on a 0–4 scale; $p = 0.03$). However, there was no discussion if these changes were clinically relevant. Improvement in quality of life based on RosaQol was also observed (score reduction by 0.6 points; $p = 0.001$), with the same caveat regarding relevance. While the most common treatment-related adverse events were infections, in line with use in psoriasis, no further details were provided. The trialists concluded that randomized controlled trials with larger sample sizes are needed to confirm their findings [48].

7.2 Erenumab

Erenumab is a human monoclonal antibody that binds to the calcitonin gene-related peptide (CGRP) receptor and is registered for the prevention of migraine. CGRP is a neuropeptide that modulates nociceptive signaling and vasodilatation. An open-label phase II study to evaluate the efficacy and tolerability of erenumab (AMG 334) 140 mg subcutaneously at a 4-week interval for persistent redness and flushing of rosacea was initiated in June 2020 and is expected to be completed in August 2021 [49].

7.3 B244 Topical Spray

B244 is a topical spray of a single bacterial strain of *Nitrosomonas eutropha (N. eutropha) D23*. This bacterium converts ammonia and urea from sweat into nitrite, which has antibacterial properties, and into nitric oxide, which regulates inflammation and vasodilation. B244 in a topical spray for erythema and telangiectasia in rosacea was evaluated in an 8-week, randomized, vehicle-controlled phase II trial. The study was completed in 2019, but no results have been posted [50].

8 Omiganan Topical Gel

The efficacy and safety of omiganan pentahydrochloride, a synthetic, antimicrobial peptide, in a topical gel was evaluated in four studies in patients with inflammatory lesions in rosacea [51–54]. The last study was completed in April 2018 [54]. However, no results have been published.

9 Rifaximin

Rifaximin is a nonabsorbed, gut-active, oral antibiotic registered for traveler's diarrhea, irritable bowel syndrome, and hepatic encephalopathy. Associations between rosacea and gastrointestinal disease have been previously described. A study evaluating the role of small intestinal bacterial

overgrowth (SIBO) in patients with rosacea demonstrated that eradication of SIBO with rifaximin 400 mg three times daily for 10 days resulted in complete resolution of rosacea features in 78% of patients [55]. A later pilot study aimed to determine the prevalence of SIBO in patients with rosacea attending a gastroenterology clinic. Half of the 63 patients (51%) were diagnosed with SIBO, compared with 23% of general population controls and 5% of healthy subjects. Patients with rosacea and SIBO received rifaximin 400 mg three times daily for 10 days. Of these, 46% reported clearly or markedly improved rosacea, 25% reported moderate and 11% mild improvement [56].

A phase II, randomized controlled trial to investigate the safety and efficacy of oral rifaximin delayed-release versus placebo in 236 adults with moderate-to-severe papulopustular rosacea and positive lactulose H2/CH4 breath test started in June 2018 and was to be completed in October 2020, but no results have been posted [57].

10 DMT210 5% Topical Gel

DMT210 topical gel was developed to downregulate the cutaneous proinflammatory cytokines responsible for the inflammation and redness in rosacea. DMT210 blocks TLR-2 and G-protein coupled receptor signaling, which might inhibit IL-6 and TNF-α expression. The efficacy, safety, and tolerability of twice-daily dosing of DMT210 5% gel in 104 patients with moderate to severe rosacea was evaluated in a 12-week, phase II, multi-center, double-blind, vehicle-controlled trial. The study was completed in April 2018, but no results have been published [58]. An ophthalmic formulation will also be developed for treating ocular rosacea.

11 Hydroxychloroquine

Hydroxychloroquine is an anti-malaria drug that has been used widely to treat patients with systemic autoimmune diseases (e.g., rheumatoid arthritis and systemic lupus erythematosus). Hydroxychloroquine has an immune-modifying role by reducing pro-inflammatory cytokine production and modulation of certain costimulatory molecules. A recent study in a mouse model of rosacea demonstrated that hydroxychloroquine inhibited pro-inflammatory factors as well as mast cell proteases [59]. In an additional trial of six adult patients with moderate to severe rosacea treated for 8 weeks with hydroxychloroquine 200 mg twice daily, success rates were 67% for inflammatory lesions (reaching IGA score 0 or 1) and 83% for erythema (reaching a clinician's erythema assessment [CEA, ranging 0–4] score of 0 or 1) [59]. There were no adverse events. A recent, multicenter, randomized, double-blind, phase IV pilot study in 66 patients with rosacea (type not specified), compared hydroxychloroquine 200 mg twice daily with doxycycline 100 mg once daily (and a placebo once daily) [60]. CEA success was defined as a decrease of at least 1 point and IGA success as a score of 0 or 1. Fifty-eight patients completed the 8-week study, and similar improvements were seen in erythema (89.3% for hydroxychloroquine vs 86.7% for doxycycline: $p = 0.193$) and papules (82.1% vs 93.3%, respectively; $p = 0.555$). In the hydroxychloroquine group, 28.5% of the participants reported adverse events, compared with 33.3% in the doxycycline group. The most common events were dry skin, dry eyes, and dizziness in the hydroxychloroquine group, and dry skin and flatulence in the doxycycline group. However, long-term hydroxychloroquine use can cause irreversible retinopathy, a well-known serious adverse event [61].

12 Conclusion

Updating the diagnostic approach to rosacea focussing on individual features has led to advances in understanding of pathophysiology, treatment approaches, and ultimately patient care. New treatments for rosacea have been developed in three ways—greater understanding of pathophysiology; development of novel topical modalities for active interventions previously known to be effective in rosacea; and repurposing treatments used in other dermatologic conditions for rosacea. These therapeutic advances expand treatment options and could improve outcomes in rosacea patients. Nevertheless, while achievement of complete or almost complete clearance of rosacea features is the goal, not all patients achieve these outcomes presently, despite treatment adherence. Thus, there is still an ongoing need for more efficacious treatments, including those used in combination, to achieve this outcome. Finally, current treatment approaches have almost exclusively focused on only two features of rosacea—erythema and papules/pustules. Ocular rosacea and phyma, including medical interventions for early inflammatory phases of the latter, have largely been neglected. To comprehensively address the needs of all patients with rosacea, further advances in pathophysiology and treatments are awaited.

Author contributions EJZ, BWMA and SV performed the literature search. EJZ, BWMA, SV and JT drafted the paper. MMDL and ZF critically revised the work.

Declarations

Funding No funding was received for the preparation of this review.

Conflict of interest EJ v Z, MMD vd L, BWMA, SV and ZF: none. JT: advisor, consultant, investigator and/or speaker and has received honoraria and grants from Almirall, Alfasigma, Bausch Health, Boots-Walgreens, Botanix, Cipher, Galderma, L'Oreal, Promius, Sun.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent to publish Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

References

1. van Zuuren EJ. Rosacea. N Engl J Med. 2017;377:1754–64.
2. Tan J, Almeida LM, Bewley A, *et al*. Updating the diagnosis, classification and assessment of rosacea: recommendations from the global ROSacea Consensus (ROSCO) 2019 panel. Br J Dermatol. 2017;176:431–8.
3. 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.
4. Schaller M, Almeida LMC, Bewley A, *et al*. Recommendations for rosacea diagnosis, classification and management: update from the global ROSacea Consensus 2019 panel. Br J Dermatol. 2020;182:1269–76.
5. van Zuuren EJ, Fedorowicz Z, Tan J, *et al*. Interventions for rosacea based on the phenotype approach: an updated systematic review including GRADE assessments. Br J Dermatol. 2019;181:65–79.
6. Tan J, Berg M. Rosacea: current state of epidemiology. J Am Acad Dermatol. 2013;69(Suppl 1):S27-35.
7. Tan J, Schöfer H, Araviiskaia E, *et al*. Prevalence of rosacea in the general population of Germany and Russia—the RISE study. J Eur Acad Dermatol Venereol. 2016;30:428–34.
8. Gether L, Overgaard LK, Egeberg A, Thyssen JP. Incidence and prevalence of rosacea: a systematic review and meta-analysis. Br J Dermatol. 2018;179:282–9.
9. Alexis AF, Callender VD, Baldwin HE, *et al*. Global epidemiology and clinical spectrum of rosacea, highlighting skin of color: Review and clinical practice experience. J Am Acad Dermatol. 2019;80:1722–9.
10. Baldwin HE, Harper J, Baradaran S, Patel V. Erythema of rosacea affects health-related quality of life: results of a survey conducted in collaboration with the National Rosacea Society. Dermatol Ther (Heidelb). 2019;9:725–34.
11. Halioua B, Cribier B, Frey M, Tan J. Feelings of stigmatization in patients with rosacea. J Eur Acad Dermatol Venereol. 2017;31:163–8.
12. Haber R, El Gemayel M. Comorbidities in rosacea: A systematic review and update. J Am Acad Dermatol. 2018;78:786–92.
13. Gallo RL, Granstein RD, Kang S, *et al*. Rosacea comorbidities and future research: the 2017 update by the National Rosacea Society Expert Committee. J Am Acad Dermatol. 2018;78:167–70.
14. Holmes AD, Spoendlin J, Chien AL, *et al*. Evidence-based update on rosacea comorbidities and their common physiologic pathways. J Am Acad Dermatol. 2018;78:156–66.
15. Buddenkotte J, Steinhoff M. Recent advances in understanding and managing rosacea. F1000Res. 2018;7:1885.
16. Steinhoff M, Schauber J, Leyden JJ. New insights into rosacea pathophysiology: a review of recent findings. J Am Acad Dermatol. 2013;69:S15-26.
17. Chang ALS, Raber I, Xu J, *et al*. Assessment of the genetic basis of rosacea by genome-wide association study. J Investig Dermatol. 2015;135(6):1548–55.
18. Holmes AD. Potential role of microorganisms in the pathogenesis of rosacea. J Am Acad Dermatol. 2013;69:1025–32.
19. Yamasaki K, Kanada K, Macleod DT, *et al*. TLR2 expression is increased in rosacea and stimulates enhanced serine protease production by keratinocytes. J Investig Dermatol. 2011;131:688–97.
20. Woo YR, Lim JH, Cho DH, Park HJ. Rosacea: molecular mechanisms and management of a chronic cutaneous inflammatory condition. Int J Mol Sci. 2016;15(17):1562.
21. Kelhälä HL, Palatsi R, Fyhrquist N, *et al*. IL-17/Th17 pathway is activated in acne lesions. PLoS ONE. 2014;9:e105238.
22. Schwab VD, Sulk M, Seeliger S, *et al*. Neurovascular and neuroimmune aspects in the pathophysiology of rosacea. J Investig Dermatol Symp Proc. 2011;15:53–62.
23. 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 Dermatol. 2002;46:584–7.
24. Tan J, Steinhoff M, Berg M, *et al*. Shortcomings in rosacea diagnosis and classification. Br J Dermatol. 2017;176:197–9.
25. 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.
26. Thiboutot D, Anderson R, Cook-Bolden F, *et al*. Standard management options for rosacea: the 2019 update by the National Rosacea Society Expert Committee. J Am Acad Dermatol. 2020;82:1501–10.
27. 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.
28. 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.
29. Gold LS, Papp K, Lynde, 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.
30. Schaller M, Kemény L, Havlickova B, *et al*. A randomized phase 3b/4 study to evaluate concomitant use of topical ivermectin 1% cream and doxycycline 40-mg modified-release capsules, versus topical ivermectin 1% cream and placebo in the treatment of severe rosacea. J Am Acad Dermatol. 2020;82:336–43.

31. Garrido-Mesa N, Zarzuelo A, Gálvez J. Minocycline: far beyond an antibiotic. Br J Pharmacol. 2013;169:337–52.
32. van der Linden MMD, van Ratingen AR, van Rappar 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.
33. Alikhan A, Kurek L, Feldman SR. The role of tetracyclines in rosacea. Am J Clin Dermatol. 2010;11:79–87.
34. Korting HC, Schöllmann C. Tetracycline actions relevant to rosacea treatment. Skin Pharmacol Physiol. 2009;22:287–94.
35. Perret LJ, Tait CP. Non-antibiotic properties of tetracyclines and their clinical application in dermatology. Australas J Dermatol. 2014;55:111–8.
36. Jackson JM, Kircik LH, Lorenz J. Efficacy of extended-release 45 mg oral minocycline and extended-release 45 mg oral minocycline plus 15% azelaic acid in the treatment of rosacea. J Drugs Dermatol. 2013;12:292–8.
37. 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.
38. Gold LS, Del Rosso JQ, Kircik L, et al. Minocycline 1.5% foam for the topical treatment of moderate to severe papulopustular rosacea: results of 2 phase 3, randomized, clinical trials. J Am Acad Dermatol. 2020;82:1166–73.
39. Webster G, Draelos Z, Graber E, *et al*. A multicentre, randomized, double-masked, parallel group, vehicle-controlled phase IIb study to evaluate the safety and efficacy of 1% and 3% topical minocycline gel in patients with papulopustular rosacea. Br J Dermatol. 2020;183:471–9.
40. Dr Reddy's Laboratories Limited. A controlled study to assess the efficacy, safety and tolerability of oral DFD-29 extended release capsules. ClinicalTrials.gov. Identifier NCT03340961. https://clinicaltrials.gov/ct2/show/NCT03340961. Accessed 4 Dec 2020.
41. 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.
42. Sol-Gel Technologies, Ltd. A study of S5G4T-1 in the treatment of papular-pustular rosacea. ClinicalTrials.gov. Identifier NCT03564119https://clinicaltrials.gov/ct2/show/NCT03564119. Accessed 1 Nov 2020.
43. Sol-Gel Technologies, Ltd. A study of S5G4T-1 in the treatment of papulopustular rosacea. ClinicalTrials.gov. Identifier NCT03448939. https://clinicaltrials.gov/ct2/show/NCT03448939. Accessed 1 Nov 2020.
44. Bhatia N, Werschler W, Baldwin H, et al. Efficacy and safety of micro-encapsulated benzoyl peroxide (E-BPO) cream, 5% in papulopustular rosacea: results from two phase 3, vehicle-controlled trials. Presented at Maui Derm for Dermatologists 2020, Maui, Hawaii, January 25–29, 2020.
45. Bhatia N, Werschler W, Baldwin H, et al. Long-term efficacy and safety of benzoyl peroxide cream, 5% prepared with micro-encapsulation in papulopustular rosacea: results from an extension of two phase 3, vehicle-controlled trials. Presented at Maui Derm for Dermatologists 2020, Maui, Hawaii, January 25–29, 2020.
46. Sol-Gel Technologies, Ltd. A long term safey study of S5G4T-1 in the treatment of papulopustular rosacea. ClinicalTrials.gov. Identifier NCT03564145. https://www.clinicaltrials.gov/ct2/show/NCT03564145. Accessed 1 Nov 2020.
47. Park B. FDA to review investigational rosacea treatment epsolay. MPR, September 14, 2020. https://www.empr.com/home/news/drugs-in-the-pipeline/benzoyl-peroxide-epsolay-for-rosacea-fda-review/. Accessed 12 Nov 2020.
48. Kumar AM, Chiou AS, Shih YH, *et al*. An exploratory, open-label, investigator initiated study of interleukin-17 blockade in patients with moderate-to-severe papulopustular rosacea. Br J Dermatol. 2020;183:942–3.
49. Messoud Ashina, Danish Headache Center. Efficacy and tolerability of erenumab in the management of persistent redness and flushing in rosacea (STOP Ros). ClinicalTrials.gov. Identifier NCT04419259. https://clinicaltrials.gov/ct2/show/NCT04419259. Accessed 15 Nov 2020.
50. AOBiome LLC. A study to determine safety and efficacy of b244 in subjects with mild to moderate rosacea. ClinicalTrials.gov. Identifier NCT03590366. https://www.clinicaltrials.gov/ct2/show/NCT03590366. Accessed 15 Nov 2020.
51. Maruho Co., Ltd. Study to evaluate the long-term safety of a once-daily omiganan topical gel. ClinicalTrials.gov. Identifier NCT02576847. https://clinicaltrials.gov/ct2/show/NCT02576847. Accessed 15 Nov 2020.
52. Maruho Co., Ltd. Study to evaluate the safety and efficacy of a once-daily CLS001 topical gel versus vehicle. ClinicalTrials.gov. Identifier NCT02576860. https://www.clinicaltrials.gov/ct2/show/NCT02576860. Accessed15 Nov 2020.
53. Maruho Co., Ltd. A twelve week safety and efficacy study in rosacea. ClinicalTrials.gov. Identifier NCT01784133. https://www.clinicaltrials.gov/ct2/show/NCT01784133. Accessed 15 Nov 2020.
54. Maruho Co., Ltd. Study to evaluate the safety and efficacy of a once-daily CLS001 topical gel versus vehicle. ClinicalTrials.gov. Identifier NCT02547441. https://www.clinicaltrials.gov/ct2/show/NCT02547441. Accessed 15 Nov 2020.
55. Parodi A, Paolino S, Greco A, *et al*. S Small intestinal bacterial overgrowth in rosacea: clinical effectiveness of its eradication. Clin Gastroenterol Hepatol. 2008;6:759–64.
56. Weinstock LB, Steinhoff M. Rosacea and small intestinal bacterial overgrowth: prevalence and response to rifaximin. J Am Acad Dermatol. 2012;68:875–6.
57. Alfasigma S.p.A. Safety and efficacy of rifaximin in patients with papulopustular rosacea and positive lactulose breath test. ClinicalTrials.gov. Identifier NCT03864978. https://www.clinicaltrials.gov/ct2/show/NCT03864978. Accessed 30 Nov 2020.
58. Dermata Therapeutics. DMT210 topical gel in the treatment of acne rosacea. ClinicalTrials.gov. Identifier NCT03003104. https://www.clinicaltrials.gov/ct2/show/NCT03003104. Accessed 12 Nov 2020.
59. Li J, Yuan X, Tang Y, *et al*. Hydroxychloroquine is a novel therapeutic approach for rosacea. Int Immunopharmacol. 2020;79:106178.
60. Wang B, Yuan X, Huang X, et al. Efficacy and safety of hydroxychloroquine for treatment of patients with rosacea: a multi-center, randomized, double-blind, double-dummy, pilot study. J Am Acad Dermatol. 2021;84:543–5.
61. The Royal College of Ophthalmologists. Clinical guidelines—hydroxychloroquine and chloroquine retinopathy: recommendations on monitoring, Jan 2020. Review date December 2020. https://www.rcophth.ac.uk/wp-content/uploads/2020/02/HCR-Recommendations-on-Monitoring.pdf. Accessed 6 Dec 2020.