An Update on Rosacea Medical Management

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OUTLINE: Rosacea is a chronic multivariant inflammatory condition with exacerbations and remissions requiring both a goal to initial improvement and a commitment to long term management of flares and maintenance therapy. Whilst various clinical manifestations of rosacea have been defined there is an evolution from isolated clinical subtype management to a phenotypic paradigm that is individually specific as patients may evolve from one subtype to another or have phenotypic features of differing subtypes at one time. Rosacea is not curable but rather controllable using a combination of topical, oral and energy-based treatments tailored to specific needs of the individual which vary in time. Quality patient education is vital to patient outcomes. Traditional consultations elevated to include video-based material and education may improve results so patients can fully understand how to manage their rosacea. The article overviews existing and emerging therapies and aims to provide current up-to-date information to enable effective acute and long-term management of rosacea.

KEYWORDS: rosacea, topical treatment, systemic treatment, lifestyle, management, phenotypes, therapy

Wines N, Alexander P, Andric S, Dawes-Higgs L, Donohue S, Harris A, Ng S, McKay C, Polcz M, O'Connor A, Tomizawa A. An Update on Rosacea Medical Management. Opin Prog Cosmet Dermatol 2021;1(2):55-66.

Introduction

Rosacea has a significant psychosocial impact on quality of life. Effective management starts with quality patient education. Both an acute management plan and a long-term plan are required. Whilst there is no cure for rosacea, clinical features are controlled using a range of topical, oral and energy-based device treatments in isolation or combination tailored to the individual's specific needs and clinical presentation which may vary in time.

There are no diagnostic laboratory tests for rosacea. Diagnosis is based on clinical and historical features. Phenotypic variants of rosacea have been defined by the National Rosacea Society and updated in 2017.[1] The original standard classification of rosacea identified the most common patterns or groupings of signs and symptoms and designated them as follows: subtype 1, erythematotelangiectatic (ET); subtype 2, papulopustular; subtype 3, phymatous; and subtype 4, ocular. The issue with this subtype classification is that the frequent simultaneous occurrence of more than one subtype and the potential progression from one subtype to another was not considered and hence an updated phenotypic classification was established (Table 1).[1] This system enables therapy to be personalized to achieve optimal outcome.

Table 1. *Phenotypes of rosacea*

Diagnostic*	Major†	Secondary
Fixed centrofacial erythema in a characteristic pattern that may periodically intensify Phymatous changes	Flushing Papules and pustules Telangiectasia Ocular manifestations: • Lid margin telangiectasia • Interpalpebral conjunctival injection • Spade-shaped infiltrates in the cornea • Scleritis and sclerokeratitis	Burning sensation Stinging sensation Oedema Dryness Ocular manifestations: • "Honey crust" and collarette accumulation at the base of the lashes • Irregularity of the lid margin Evaporative tear dysfunction (rapid tear breakup time)

* *These features by themselves are diagnostic of rosacea*

† *Two or more major features may be considered diagnostic*

Patient education and counselling

Investment in quality patient education is vital to patient compliance, satisfaction and outcome[2] and could be considered the most essential component to the medical management of rosacea. Patients with rosacea have reduced quality of life and also higher rates of psychiatric illnesses[3], both of which are improved with quality management.[3]

This management starts with education and counselling. Methods of successful education have advanced beyond traditional oral and written forms to now include audio (such as podcasts) and video means. Group education may also be effective when applied to long-term disease management such as with rosacea.[2]

It is essential to communicate the chronicity of rosacea, it's exacerbating factors and remitting nature, and the goal of initial improvement followed by long term maintenance of the condition. Education in rosacea involves a multifaceted approach. Individualised triggering factors need to be determined and understood. These triggers include the ingestion of hot foods and drinks along with alcohol, mainly red wine. Other triggers include heat, sunlight and irritating skin care products. We have found that having patients maintain a diary of their disease progress photographically on their phone as well as documenting potential triggers in the notes section of their phones is useful to help both the physician and patient understand the natural history of their rosacea. Other key factors to cover when educating patients are outlined in Table 2.

The emotional, social and professional impact of rosacea upon a patient's life needs to be established and may affect choice of treatment, with a potentially more aggressive approach selected for those in who the psychosocial impact is significant. A positive correlation between psychological intervention and dermatological disorders has been established and cannot be underestimated.[4]

Efficiency of the education process can be enabled by training supporting clinic staff, using patient information sheets, or by developing your own clinic video-based education.

Table 2. *Patient education – key points to communicate*

- Cause of rosacea
- Exacerbating and remitting nature
- Need for short term control and commitment to long term maintenance
- Potential triggers and documenting these
- The value of maintaining a photographic diary of their skin
- The different phenotypes of rosacea
- How and when to use medications consistently
- Tips to manage flares and maintain control: value of continuing topical therapy after signs and symptoms of the acute rosacea flare have resolved in order to maintain remission and prevent recurrence[5]
- An understanding of the clinical phenotypes and subtypes of rosacea
- How to use skin care*
- Tips to manage the emotional impact of rosacea

**Gentle cleansing morning and night with fingertips, avoiding scrubbing and soap cleansers. Regular use of a moisturizer is also suggested to assist in reducing epidermal barrier dysfunction that occurs in association with rosacea.*[6,7]

Lifestyle, diet and rosacea

Management of rosacea flares effectively requires the identification of individual lifestyle and environmental triggers. What affects one rosacea sufferer may not affect another. Patients commonly enquire about the influence of dietary factors on their rosacea.

A National Rosacea Society survey of over 400 patients found that 78% of rosacea sufferers had altered their diet in the attempt to manage their rosacea. Of these patients, 95% reported a reduction in symptoms.[8]

One proposed way to consider food triggers is to group them into categories including heat- related, alcohol-related, capsaicin-related and cinnamaldehyde-related. Heat-related foods include hot beverages such as tea, hot chocolate and coffee (30% report coffee to be a trigger). Alcohol is a frequent trigger and may include wine (50%) beer and spirits (42%). Capsaicin is found in spicy foods (75%) and includes sauces, cayenne and red peppers. Lastly, cinnamaldehyde is found in a range of foods some of which include tomatoes, chocolate and citrus.[9] Niacin-containing foods such as turkey, peanut, tuna, liver and chicken have also been reported to cause flushing.[10]

Dairy products (yoghurt, sour cream, cheese but not cottage cheese), chocolate and vanilla, soy sauce, yeast extracts (but not bread), vinegar, eggplants, avocado, spinach, beans (lima, navy or pea), bananas, red plums, raisins and figs may also exacerbate symptoms in some patients.[11] A recent case-control study of 1347 Chinese patients with rosacea and 1290 matched controls found that high-frequency intake of fatty food and tea resulted in exacerbation of rosacea. High fat intake was associated with ET and phymatous rosacea, whilst tea was only associated with ET rosacea. Dairy products showed negative correlations with ET rosacea and papulopustular rosacea.[12]

Dietary pathogenesis of symptoms is believed to be via the transient receptor potential vanilloid 1 (TRVP1), also known as the capsaicin receptor. This is located on sensory nerves and keratinocytes, and is activated by sun exposure, hot drinks, alcohol, spicy foods, vanilla, cinnamon, and caffeine. Transient receptor potential ankyrin receptor 1 (TRPA1) is located on perivascular sensory neurons in the dermis and is activated by cold temperature and formalin-containing foods (crustaceans, noodles, tofu, shitake mushroom). When activated, these receptors release substance P and calcitonin gene-related peptide which induce a transient inflammatory response. Calcitonin gene-related peptide dilates arterioles, whereas substance P particularly affects post-capillary venules, resulting in flushing and oedema.[10]

Dietary micronutrient supplementation

Currently there is no convincing evidence that specific nutrients alleviate rosacea symptoms however further research is warranted in the case of zinc and omega-3 fatty acids.[9]

Zinc is fundamental for the innate immune system and acts as an antioxidant and anti-inflammatory molecule. It has shown benefit in other cutaneous inflammatory disorders but, to date, evidence for zinc supplementation in rosacea has shown conflicting results. One trial noted improvement of rosacea after dietary supplementation of zinc sulphate 100 mg three times daily.[13] Omega-3 fatty acids are polyunsaturated fatty acids including eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and alpha linoleic acid (ALA). They are substrates for prostaglandins that inhibit pro-inflammatory pathways. One randomised control trial found a statistically significant improvement in subjects with rosacea who ingested 325 mg of EPA and 175 mg EPA twice daily for three months.[14]

The skin-gut axis

The skin-gut axis proposes an inherent link between gut dysbiosis and inflammatory skin disease.[10] Population-based studies have highlighted an increased risk of rosacea in patients with certain gastrointestinal diseases such as coeliac disease, *Helicobacter pylori* infection, inflammatory bowel disease and irritable bowel syndrome. Small intestinal bacterial overgrowth (SIBO) is 2–20 times greater in rosacea patients than the general public.[10] Eradication of *H. pylori* and SIBO in patients via antibiotic administration has resulted in resolution of rosacea symptoms compared to placebo.[15]

Microbiome diversity established with probiotics or fermented foods (such as kefir or kimchi) have also been shown to hasten clearance of *H. pylori* and resulted in improvement of rosacea.[16] Probiotics are an attractive therapeutic avenue given their relatively low side effect profile. Further research is required however, as probiotic use does not necessarily lead to growth of favourable gut microorganisms.[15] Furthermore, their effect has shown to be short-lived after cessation of supplementation. The effect of different strains of probiotics for different conditions merits further research.[16] Whether or not diet can influence microbial dysbiosis has yet to be defined in rosacea.

When treating patients with rosacea, consider the individual nature of a patient's triggers, as well as the impact of long-term antibiotic use on gut microflora. Prebiotics, fibre-rich foods from plant sources, supporting the growth of healthy gut microorganisms, and the importance of a healthy diet for general health as well as skin health cannot be overstated.

Topical and systemic treatment of rosacea

Patients are often treated with a combination of therapies including topical and oral agents simultaneously with or without laser or light devices. The selection of treatment is influenced by the clinical phenotype, severity of rosacea, psychosocial impact of the disease and physician experience.

Prior to commencing treatment, we highly recommend pre-treatment and progressive photos (front, oblique left and right views) be taken using standardised photography to monitor progress. We find patients do not recall their improvement with treatment and we find this improves their satisfaction with treatment.

Mild inflammatory papulopustular rosacea is usually initially managed with topical therapy alone. More significant rosacea requires a combination of topical and oral therapy (plus or minus energy-based devices). It has long been known that after discontinuing conventional therapy, one-fourth of patients relapse after one month and two-thirds relapse after six months.[17] A long term plan for management of recurrence needs to be established. Often topical therapy is prescribed to maintain remission. If topical therapy alone does not sustain control, intermittent oral treatment is usually required. Severe variants of inflammatory rosacea requiring multiple courses of antibiotics to achieve improvement may require consideration of oral retinoid therapy.

Certain circumstances can make management difficult. Such as when treatment is contraindicated or during pregnancy. Pregnancy can result in exacerbation of rosacea or the appearance of rosacea for the first time and proposes a therapeutic dilemma as many traditional therapies are contraindicated. This is covered in more detail below.

The use of energy-based devices for rosacea is covered elsewhere within this edition. Device use is determined by availability of equipment and physician experience. In our experience combined medical and energy based light treatment leads to enhanced patient outcomes and prolongation of results and remission. Laser intervention is sometimes seen as aesthetic rather than as an important continuum in patient medical management. The extent to which lasers prevent recurrence and sustain remission is yet to be determined in a formal study.

An overview of existing and emerging therapies follows aiming to provide current up to date information to enable effective selection of treatment for individual patients.

Standard topical therapy

Metronidazole

Topical 1% metronidazole cream has a long history of safety and efficacy in the treatment of papulopustular rosacea backed by multiple blinded randomised vehicle-controlled trials.[18-21] Topical metronidazole is thought to exhibit anti-inflammatory properties by reducing generation of reactive oxygen species.[22] Metronidazole 0.75% cream and 0.75% gel is marketed as Rozex in Australia and has Therapeutic Goods Administration (TGA) approval. It is recommended to be applied twice a day for up to 3-4 months and is safe in pregnancy.

Azelaic acid

Topical 15% azelaic acid gel, foam and 20% azelaic acid cream has also been shown to be efficacious in multiple blinded randomised vehicle-controlled trials for the treatment of papulopustular rosacea.[23] It also has a long safety record but may be more irritating than topical metronidazole.[24] Azelaic acid has antimicrobial and anti-inflammatory properties and inhibits follicular keratinization.[23] In comparison, trials of daily topical metronidazole, 15% azelaic acid gel twice daily was shown to be similar in efficacy to 1% metronidazole gel but superior to 0.75% metronidazole gel.[25,26] In Australia 15% azelaic acid gel and 20% azelaic acid lotion are approved by the TGA and are marketed as Finacea and Azclear lotion, respectively, and are safe to use during pregnancy.

Ivermectin

Topical 1% ivermectin cream is a novel treatment for papulopustular rosacea. It has both acaricidal and anti-inflammatory actions against Demodex mites.[27] Ivermectin 1% cream is applied to facial skin daily for up to 12 weeks. In two randomised, controlled, double blind, vehicle-controlled pivotal studies ivermectin 1% cream achieved treatment success in 38.4% and 40.1% of subjects.[28] In an industry sponsored blinded randomised controlled trial of 962 participants daily 1% ivermectin cream was shown to be more efficacious than twice daily topical 0.75% metronidazole cream for papulopustular rosacea and had better tolerability.[29] Mild stinging and burning can occur on application. In Australia ivermectin is marketed as Soolantra and is Category C in pregnancy.

Sodium sulfacetamide

A series of eight patients with papulopustular rosacea showed an improvement with topical 10% sodium sulfacetamide and 5% sulphur foam.[30] Topical 10% sodium sulfacetamide and 5% sulphur foam combined with sunscreen (Rosac cream) was shown to be more beneficial than 0.75% metronidazole cream for papulopustular rosacea and erythema but it was noted 7 out of 75 of those treated with the combination had poor tolerance because of possible sulphur drug

allergy.[31] Sodium sulfacetamide is not approved by the TGA and is not available in Australia.

Clindamycin

In a randomised vehicle-controlled trial involving 629 participants with papulopustular rosacea, topical 1% cream and 0.3% cream were no more effective than placebo.[32] Topical clindamycin is neither approved by the TGA in Australia nor the FDA.

Retinoids

There is limited evidence for the use of topical retinoids in the management of papulopustular rosacea. A small randomised controlled study comparing topical tretinoin 0.025% cream and low dose isotretinoin (10 mg/day) in 22 subjects over 16 weeks reported benefit in both treatment groups. However, the rate of improvement was more rapid in the oral isotretinoin group.[33]

Permethrin

Topical 5% permethrin gel was compared to placebo in 20 patients with papulopustular rosacea in a split face randomised trial. Blinded analysis at 12 weeks showed an improvement in Demodex mite density although both sides showed improvement in symptoms.[34] In another randomised controlled trial of 63 patients with papulopustular rosacea twice daily topical 5% permethrin had a similar benefit to daily 0.75% topical metronidazole gel.[35]

Pimecrolimus

Two randomised vehicle-controlled trials showed no benefit of topical pimecrolimus in patients with papulopustular rosacea.[36,37] One randomised open-label trial showed topical 1% pimecrolimus was no better than 1% metronidazole cream.[38] Interestingly there have been reports of topical pimecrolimus and topical tacrolimus causing rosacea-like eruptions.[39,40]

Dapsone

Topical dapsone is a sulfone antibacterial with anti-inflammatory actions. Whilst previously approved, it is no longer available in Australia unless compounded. Dapsone 7.5% gel is applied once daily for up to 12 weeks. It should be avoided in those with known glucose-6-phosphate dehydrogenase deficiency.[41]

Brimonidine

Brimonidine tartrate is a potent vasoconstrictor and a highly selective alpha-2 adrenergic receptor agonist used to reduce facial redness in rosacea. It is available as a 0.33% gel that is applied once daily exhibiting a response within 30 minutes of application.[42] In a 1-year open label study the safety and consistent efficacy of using 0.5% brimonidine gel was demonstrated in the long-term treatment of moderate to severe erythema.[43] Adverse effects include burning dysaesthesia, flushing, worsening erythema and contact dermatitis. A paradoxical erythema reaction with chronic use of topical brimonidine 0.33% gel has been reported.[44]

Oxymetazoline

Oxymetazoline hydrochloride is a primary alpha-1a agonist that lessens persistent facial erythema associated with rosacea through vasoconstriction of the cutaneous microvasculature. It is available as a 1% cream that is applied topically to facial skin daily. Reported side effects include application-site dermatitis, paraesthesia, pruritus and pain.[45] In the open label REVEAL trial 36.7% of patients achieved a 2-grade or greater composite improvement from baseline in Clinician Erythema Assessment and 43.4% in Subject Self-Assessment at 52 weeks. Only 0.7% of patients experienced a rebound effect.[45]

Combination topical therapy

Clindamycin and tretinoin

A small randomised placebo-controlled trial of 30 rosacea patients found a combined clindamycin 1.2% and tretinoin 0.025% gel to be effective in reducing papulopustular lesions, but not in decreasing in facial erythema.[46] Another randomised, double blind, placebo-controlled pilot study involving 79 subjects with moderate-to-severe papulopustular rosacea using a combined clindamycin 1.2% and tretinoin 0.025% gel did not find a significant difference in papule and pustule count between study groups after 12 weeks.[47] A significant improvement in the telangiectatic component of rosacea was however reported.

Clindamycin and benzoyl peroxide

A single randomised, double-blind, vehicle-controlled trial of 53 patients with moderate-to-severe rosacea evaluated a daily application of a fixed combination 5% benzoyl peroxide and 1% clindamycin gel over 12 weeks.[48] A 71.3% reduction in papule and pustule count was reported for the intervention group. Decreased severity scores for erythema, flushing/blushing, and papules/pustules were also reported for the treatment group.[48]

Permethrin and tea tree oil

A single randomised, double-blind, controlled study of 35 patients with papulopustular rosacea evaluated permethrin 2.5% in combination with tea tree oil in a topical gel applied twice daily over a 12-week period. A reduction in Demodex mite density and clinical manifestations including papules, pustules and non-transient erythema were reported in the intervention group.[49]

Emerging topical therapies

Topical minocycline

In a recent randomised controlled trial enrolling 1522 patients, a novel topical minocycline 1.5% foam was used to treat patients with moderate-to-severe papulopustular rosacea. Participants applied a thin layer of the foam over all areas of the face daily for 12 weeks. There was a statistically significant reduction in the inflammatory lesion count by an average of 18 lesions versus 15 in the placebo group. There was also an improvement in the rate of Investigator Global Assessment (IGA) endpoint success achieved.[50] An open-label extension study demonstrated a favourable safety and tolerability profile for topical minocycline 1.5% foam up to 52 weeks.[51] In another randomised controlled trial with 270 patients with papulopustular rosacea and less than 40 inflammatory lesions, patients were randomised to daily 1% and 3% minocycline gel or vehicle for 12 weeks. Results showed a statistically significant difference in lesion counts with a drop of 12.6 and 13.1 lesions with minocycline 1% and 3%, respectively, versus 7.9 with the vehicle. Treated patients also had slightly higher IGA score which was statistically significant for the 3% concentration but not the 1% concentration. Both of these studies were industry sponsored.[52]

Topical tranexamic acid

A study comprising 20 patients with ET rosacea compared four sessions of topical tranexamic acid infused dressings versus topical tranexamic acid infused dressings with micro-needling; an improvement in erythema was seen in all patients.[53]

Topical benzyl benzoate and crotamiton

Benzyl benzoate and crotamiton at different concentrations were used in a retrospective observational study of 394 patients with papulopustular rosacea and demodicosis. Results showed a decrease in Demodex mite density and improvement in symptoms.[54]

Timolol

In an open-label prospective study of 58 patients with ET and papulopustular rosacea treated with daily topical 0.5% timolol maleate showed some improvement in the ET but not papulopustular component of the rosacea.[55]

8-beta glycyrrhetinic acid

8-beta glycyrrhetinic acid is a non-steroidal anti-inflammatory. A vehicle-controlled study of 24 patients with rosacea showed an improvement in erythema but not papules and pustules.[56] Another non-controlled study using the combination cream consisting of 8-beta glycyrrhetinic acid, glutathione analogue, azelaic acid and sunscreen showed an improvement in inflammatory lesions.[57]

Standard systemic therapies

Tetracyclines

Tetracycline family antibiotics, namely doxycycline and minocycline, have been a mainstay of treatment for papulopustular rosacea for five decades. They are effective in ocular, periorificial and pyoderma faciale subtypes.[58-60] Typically, a course is prescribed over 6-12 weeks, alone or combined with topical therapies. The mechanism of action is understood to be anti-inflammatory by inhibition of neutrophil migration, inhibition of multiple matrix metalloproteinases, down regulation of cytokines and scavenging for reactive oxygen species.[58]

Doxycycline

Doxycycline 50-100 mg daily is frequently a first choice as initial oral therapy. A sub-antimicrobial dose appears to be as effective with fewer associated side effects, such as vaginal candidiasis, with a reduced capacity for development of antibiotic resistance.[61,62] Sub-antimicrobial dosing refers to dosing <50 mg/day as above this level may exceed the Minimal Inhibitory Concentration (MIC) of some bacteria, exerting an antibiotic effect via the 30S subunit of the bacterial ribosome.[58,63,64]

Adverse reactions of doxycycline include dose-related photosensitivity and pill oesophagitis.[65,66] These may be managed with patient counselling in regards to photoprotection and tablet ingestion with water and staying upright. Patients with pre-existing hiatus hernia may be at higher risk but not those with gastro-oesophageal reflux disease.[67] Cautious prescription of doxycycline is recommended in severe liver disease but it is preferred over minocycline in renal failure.[68] Doxycycline should be taken with food to augment absorption.

Assessment of therapeutic effect is recommended at 6-8 weeks.[69]As metallic ions can reduce GI absorption of tetracyclines, especially in the case of ferrous sulphate and minocycline, taking a history is important.[70]

Minocycline

Minocycline may have a therapeutic advantage on account of its higher lipophilicity and subsequent penetration of the pilosebaceous unit. Minocycline is dosed at 50-100 mg once or twice daily, or sustained-action formula 1 mg/kg daily is prescribed for 4-12 weeks. The uncommon but more significant side effect profile must be weighed up when prescribing. Possible adverse effects include dyspigmentation of nailbeds, skin, teeth, bone, mucous membranes and sclera. This is mainly seen in long term therapy.[71,72] Benign intracranial hypertension is rare, but dizziness and vertigo may occur.[73] Although uncommon, drug hypersensitivity reactions and ANCA-positive vasculitis

have been reported, as well as autoimmune hepatitis and drug induced lupus.[68,71,72,74]

Tetracycline is less frequently used but can also be prescribed in a dose 250-500 mg twice daily for 4-12 weeks. Other reported tetracyclines for use in rosacea include oxytetracycline 250-500 mg daily and lymecycline 408 mg daily, but these are not readily available in Australia.

Tetracyclines as a class are pregnancy category D owing to foetal tooth discolouration after gestation >14 weeks and are excreted in low concentrations in breast milk. They are similarly avoided in children <9 years old to prevent yellow staining of teeth.[68]

Alternate antibiotic therapies for rosacea

Alternate oral antibiotics are often used in patients who have difficulty tolerating tetracyclines due to side effects of gastrointestinal upset, candidiasis and photosensitivity.

These include macrolides such as erythromycin and less commonly azithromycin, clarithromycin and clindamycin. Sulfonamide drugs such as trimethoprim/sulfamethoxazole (Bactrim) have also been used[75,76] however are less commonly prescribed due to risk of severe adverse drug reactions.

Macrolides

Like tetracyclines, the mechanism of action of macrolides relates to anti-inflammatory effects in addition to reduction of reaction oxygen species. Erythromycin, the most commonly prescribed macrolide for rosacea, inhibits pro-inflammatory cytokines such as IL-8 and decreases neutrophil oxidative bursts.[77] Erythromycin is commonly prescribed for pregnant women beyond the first trimester and can be used in breastfeeding. It is pregnancy category A. Azithromycin, which is pregnancy category B1, has fewer drug interactions than erythromycin and is less commonly prescribed. Despite this, it has proven efficacy in limited case studies with a dosing schedule of 500 mg/day for 2 weeks.[77,78]

Isotretinoin

Isotretinoin may be considered as an important adjunct to systemic treatment of the inflammatory-subtypes of rosacea. Careful patient selection is required to optimize compliance with appropriate precautions, monitoring, surveillance, and prevention due to the risk of teratogenicity in premenopausal female patients of childbearing age.

Efficacy of isotretinoin (13-cis-retinoic acid) in the treatment of rosacea has been described since 1981.[78] Larger studies have demonstrated efficacy in treatment of papulopustular rosacea; in addition, there have been case reports of effective treatment of perioral granulomatous rosacea and the prefibrotic stage of sebaceous-type rhinophyma.[79,80] Ocular rosacea has also been treated effectively with isotretinoin with no reduction in visual acuity or serious complications (n=39).[81] Treatment with isotretinoin has also been effective in rosacea fulminans (pyoderma faciale) in combination with oral prednisolone.[82]

The mechanism of action of isotretinoin is possibly due to its ability to decrease the size of sebaceous glands, reduce sebum production, and inhibition of inflammation.[79,83] Isotretinoin has also been shown to reduce facial cutaneous blood flow by means of laser-Doppler at 10 weeks.[79]

Rademaker et al. demonstrated that very low-doses of isotretinoin (e.g. 10-20 mg once to five times a week, equivalent to 5 mg/day) has also shown to be effective for mild to moderate papulopustular rosacea (n=52).[84] In a recent randomised controlled trial (n=156), dosing of 0.25 mg/kg/day for a minimum of 4 months resulted in 57% of isotretinoin recipients reaching the primary endpoint of 90% reduction of the number of papules/pustules compared with baseline.[85] A large-scale randomised multicentre trial in 2010 (n=573) found that 24% of patients treated with isotretinoin 0.3 mg/kg/day achieved remission, compared with 13.6% of doxycycline-treated patients.[86] With a daily dose of 0.3 mg/kg for recalcitrant papulopustular rosacea, a minimum of 3-to-4 months duration of therapy is often required.

Given that symptoms often recur after ceasing isotretinoin therapy, continuous microdosing (CMI) may be considered in patients who prefer to avoid relapse upon discontinuation. In a case control study (n=12), patients were initially treated with isotretinoin 10-20 mg daily over 4 to 6 months. Oral isotretinoin was then reduced to CMI ranging from 0.03 mg to 0.17 mg/kg/day (mean 0.07 mg/kg/day). The efficacy of CMI was well-demonstrated by low mean post-treatment DLQI scores in the treatment group. Three patients were on CMI for longer than 30 months, and mean cumulative annual doses ranged from 11 to 62 mg/kg (mean 24.4 mg/kg).[87]

Agents for flushing: clonidine, propranolol, carvedilol

Treatment of ET rosacea associated with severe flushing and persistent erythema is challenging. Treatment options historically have included beta-adrenergic blockers, alpha-adrenergic blockers e.g.,

clonidine, opiate antagonists (naloxone), serotonin antagonists (ondansetron) and endoscopic thoracic sympathectomy.[88]

Beta-adrenergic blockers (carvedilol, nadolol, propranolol) can suppress flushing reactions but are limited by side effects of bradycardia, bronchospasm and hypotension in a rosacea population who are normally normotensive. A case series was reported of refractory ET rosacea effectively treated with low dose carvedilol with a reduction in cheek temperature and visual analog score within 3 weeks of therapy.[89]

Alpha-adrenergic receptor agonists such as clonidine are another agent used to reduce flushing and malar hyperthermia as an off-label use for patients whose predominant feature is flushing. However topical alpha2 agonists are generally preferred being more targeted and associated with less risk of systemic side effects. Topical brimonidine can reduce erythema for a maximum of 12 hours via direct cutaneous vasoconstriction but has been linked with rebound erythema post treatment and is not generally effective against established telangiectasias.[90]

Emerging non topical therapies

Hydroxychloroquine

In a pilot study of 66 patients with papulopustular rosacea patients were randomised to receive either hydroxychloroquine 200 mg twice daily, doxycycline 100 mg daily or placebo. Blinded review at 8 weeks showed hydroxychloroquine was non-inferior in terms of quality-of-life measures but measures of erythema were inconclusive.[91] A pilot study of oral sarecycline, an oral tetracycline antibiotic approved for acne by the FDA for the treatment of papulopustular rosacea, showed the drug was effective, safe, and well-tolerated for treating papulopustular rosacea with superior efficacy compared to controls at 12 weeks.[92]

Unpublished studies

A phase I trial of secukinumab was recently completed for papulopustular rosacea after research investigated the role of IL-17 in the pathogenesis of rosacea.[93] Subcutaneous injections of erenumab, a monoclonal antibody against calcitonin gene-related peptide receptor is currently recruiting to demonstrate effectiveness for ET rosacea and a placebo-controlled study of rifaximin, an antibiotic, is currently recruiting, although a similar trial was withdrawn in 2014.

To summarise, there are a variety of topical and oral treatments available for rosacea. Selection of treatment combinations is determined by the underlying phenotype of rosacea. Table 3 outlines current treatment options.

Table 3. *Treatment options for rosacea based on clinical features*

Treatment Option	Papulopustular	Telangiectasia	Flushing	Phyma
Topicals				
Metronidazole	✓			
Azelaic acid*	✓			
Ivermectin	✓			
Sodium sulfacetamide	✓			
Clindamycin*	✓			
Retinoids	✓			✓
Permethrin	✓			
Pimecrolimus	✓			
Dapsone	✓			
Brimonidine		✓	✓	
Oxymetazoline		✓	✓	
Combined topicals				
Clindamycin 1% + benzoyl peroxide 5%*	✓			
Oral therapy				
Doxycycline	✓			
Minocycline	✓			
Isotretinoin	✓			
Azithromycin	✓			✓
Trimethoprim	✓			
Sulfamethoxazole	✓			
Beta-adrenergic blockers (carvedilol, nadolol, propranolol)			✓	
Alpha-adrenergic blockers			✓	
Energy based device**		✓	✓	✓

**safe in pregnancy*

*** covered elsewhere in this edition*

Rosacea management during pregnancy

Pregnancy poses a therapeutic dilemma given most of the recognised and effective treatments for rosacea including tetracycline antibiotics and many of the topical therapies are all contraindicated or relatively contraindicated during pregnancy.[94] Tetracyclines are associated with discolouration of the teeth and impaired bone growth, isotretinoin is associated with congenital anomalies, and metronidazole is not recommended before the second trimester.

Due to the above concerns, there is an incorrect assumption that rosacea cannot be managed effectively during pregnancy, leaving many women untreated until postpartum resulting in considerable physical, emotional and social implications. We believe with careful education regarding skin care, safe topical therapy and in some cases safe oral therapy it is possible to gain control of rosacea during pregnancy.

To our knowledge there are no specific guidelines or trials relating to the course of rosacea or management during pregnancy. In our experience rosacea can occur for the first time in pregnancy and certainly pre-existing rosacea can flare substantially during pregnancy and for some patients may continue whilst breastfeeding. There are case reports for rosacea fulminans during pregnancy.[95-97]

Given the lack of evidence we can only share our approach to treatment. For mild-to-moderate rosacea we commence treatment with topical therapy. Topical azelaic acid is safe in pregnancy, has anti-inflammatory properties and the added benefit of reducing post-inflammatory hyperpigmentation which can occur in patients with Fitzpatrick type 3 and above skin. About 4% of the drug is absorbed systemically when applied topically.[94,98] Topical dapsone, salicylic acid and benzoyl peroxide are category C medications and hence we avoid using these. Topical clindamycin is safe in pregnancy and can also be tried.[94,98]

For those non-responsive to topicals or with more severe disease oral therapies may need to be considered. Erythromycin is a macrolide and as mentioned previously is a category A medication. It crosses the placenta poorly; hence low concentrations are expected in foetal tissue. Erythromycin is generally considered safe during any stage of pregnancy when administered for a few weeks.[99] There is a risk of pyloric stenosis with erythromycin. Azithromycin (category B1) is an alternate option, but there is less available safety data than erythromycin.[94]Amoxicillin use in the first trimester is associated with a risk of cleft palate.[100] Cephalexin has not been associated with foetal defects in animal studies, with inadequate controlled data from human subjects.[101] Trimethoprim exposure in the first trimester results in double the risk of miscarriage.[102]

Due to the lack of extensive guidelines and information there is little to go with by way of understanding the safe duration of therapies or the effect of chronic use of antibiotics on the foetus. First trimester use is best avoided and oral therapy limited to 4-6 weeks is likely to be sensible.

The value of physical therapies such as safe chemical peels and light emitting diode blue and red light laser therapies during pregnancy has not been established but in our experience have been helpful.

Studies examining the use of glycolic acid peels in human pregnancy have not been conducted. Using topical glycolic acid during pregnancy should not be of concern, as only a minimal amount is expected to be absorbed systemically.[103]

A number of large studies have been published in which researchers examined the outcomes of women who had taken low-dose acetylsalicylic acid during pregnancy and there was no increase in the baseline risk of adverse events, such as major malformations, preterm birth, or low birth weight. No studies have been conducted in pregnancy on topical use of salicylic acid however, as such a relatively small proportion is absorbed through the skin, it is unlikely to pose any risk to a developing baby.[104]

Light emitting diode (LED) is considered safe in pregnancy. LED combined with photodynamic therapy has been demonstrated to be effective for rosacea,[105] however aminolevulinic acid is classified as pregnancy category C. There are recent case reports demonstrating that coupled blue and red diode therapy is effective for papulopustular rosacea.[106] The benefit of LED for rosacea in pregnancy requires more study but is an interesting option given the degree to which treatments are contraindicated in pregnancy.

CONCLUSION

The goal of managing rosacea effectively is to focus on initial improvement as well as a planned commitment to long term management of flares and maintenance therapy. Management focuses on a phenotypic paradigm that is individually specific as patients may evolve from one subtype to another or have phenotypic features of differing subtypes at one time. A combination of topical, oral and energy-based treatments tailored to specific needs of the individual which vary in time leads to control of the condition. Quality patient education is vital to patient outcomes. The article overviews existing and emerging therapies and aims to provide current up-to-date information to enable effective acute and long-term management of rosacea.

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