Treatment options in the management of rosacea

Noreen Cowley MRCP

Rosacea can be triggered by many factors, and lifestyle advice, trigger avoidance and skin care should underpin drug treatment. Here, the author discusses the clinical subtypes of rosacea and the treatment options.

Rosacea is a common chronic inflammatory dermatitis characterised by flushing and a spectrum of clinical signs including persistent central facial erythema, telangiectasia and an inflammatory papulopustular eruption. The disorder usually presents between the ages of 30 and 50 years, although many patients recall episodes of flushing years prior to presentation. Women are affected more commonly than men. It is most frequently observed in the fair-skinned but can be seen in all skin types.

The prominent visibility of the skin changes can impact significantly on the individual’s quality of life. Over 80 per cent of patients with more severe rosacea reported that it impacted negatively on their work place interactions and over 50 per cent missed work because of their skin condition.1 As well as the embarrassing appearance of the skin, patients often report sensitive skin with symptoms ranging from burning and itching to stinging and pain.

Aetiology
The cause of rosacea is unknown. Epidemiological studies indicate a genetic predisposition but no specific rosacea gene has been identified.

Environmental exposures are reported to exacerbate rosacea. In a large survey conducted in the USA patients reported several factors that triggered their rosacea (see Table 1). Of these the top ranked was sun exposure and 70 per cent reported experiencing a flare-up related to emotional stress at least once per month.1

Until recently there has been very little study of the disease. However, the application of current molecular biology techniques is allowing the identification of several different molecular inflammatory pathways in rosacea.

An emerging hypothesis is that of an exaggerated innate immune response. Patients with rosacea are found to have increased expression of Toll-like receptor 2 (TLR2) in their skin.2 These are genetically coded detection systems that are triggered by a number of different environmental stimuli such as ultraviolet light, microbes and physical and chemical trauma.

Once triggered they activate the innate immune system producing an increase in cathelicidins and other inflammatory serum proteases producing inflammation with new vessel formation and telangiectasia.

Figure 1. Erythematotelangiectatic rosacea is the most common subtype and the most difficult to treat; topical and oral antibiotics offer limited benefit in treating background erythema.
Rosacea

Clinical subtypes

Rosacea develops gradually. It typically affects the central convexities of the face, nose, medial cheeks, forehead and chin with a predilection for the nose in men. Skin may be rough or dry and may show evidence of solar damage.

In April 2002 an expert committee explicitly defined and classified rosacea into four clinical subtypes based on specific clinical signs and symptoms (see Table 2). However, any one patient may show features of more than one subtype.

Erythematotelangiectatic

Erythematotelangiectatic rosacea (ETR) is the commonest type (see Figure 1). Patients report persistent erythema with prolonged episodes of flushing often accompanied by a burning or stinging sensation. This group frequently report sensitive skin that is intolerant of many skin products.

Examination reveals confluent erythema affecting the forehead, cheek and nose with sparing of the chin. Closer examination with magnified light reveals telangiectasia in these areas. To date, this clinical subtype has been the most difficult to treat.

Papulopustular rosacea

Papulopustular rosacea (PPR) may look like ETR with background redness but is characterised by inflammatory papules and pustules on the cheeks and nose, and in some cases forehead and chin (see Figure 2). Many of these patients come with a self-diagnosis of acne but the classic comedones of acne are absent.

This subtype shows the best and often dramatic clinical response to treatment that is gratifying for the patient and doctor.

Phymatous rosacea

Phymatous rosacea is characterised by thickening of skin with irregular surface nodularities. It most often affects the nose (rhinophyma) but may also involve other areas such as the chin, forehead and ears (see Figure 3).

Ocular rosacea

The estimated risk of ocular rosacea varies from less than 10 per cent to more than 50 per cent in different studies. Most patients will have concomitant cutaneous signs of rosacea, but in a small number the ocular manifestations may precede the cutaneous changes.

Severity of ocular rosacea is not proportional to the severity of the facial rosacea. It manifests as blepharitis, conjunctival hyperaemia, telangiectasia of the conjunctiva and lid margins, dry eyes and ocular discomfort. The patient often gives a history of ‘styes’, irritability or intolerance of contact lenses.

The cause of ocular rosacea is poorly understood and it is frequently undiagnosed. Patients are often unaware so it is important that the clinician enquires specifically with regard to ocular symptoms.

Management

The goal of treatment is to reduce morbidity and prevent complications. Current medical management is generally directed at the subtype of rosacea and includes both topical and systemic agents. However, because rosacea can have a significant impact on quality of life, any treatment plan should also be directed towards achieving improvement in general well-being.

Typically, rosacea waxes and wanes. Patients may have significant periods of freedom from lesions, though in practice many have two to three attacks per year. As it is a chronic disease rosacea requires long-term treatment and it is important that patients are made aware of this from the outset.

In all forms of rosacea it is important to identify and limit exacerbating stimuli and council avoidance. In most patients sun exposure is a trigger.

Basic skin care

It is important to discuss basic skin care, especially in patients with ETR. The use of daily sunscreen is recommended for all patients. A sunscreen that protects against UVA and B should be selected (sun protection factor >15). Physical sunscreens that contain titanium dioxide and zinc oxide are better tolerated.

The patient should be encouraged to use nonirritating formulations wherever possible. For skin cleansing a mild agent should be used and the patient advised to avoid astringents, toners, waterproof cosmetics requiring solvents for removal or products containing sodium lauryl sulphate.

The use of moisturisers should be encouraged both to improve barrier

Table 1. The commonest triggers of rosacea according to a survey conducted by the US National Rosacea Society

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<th>Trigger</th>
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<tr>
<td>Sun exposure</td>
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<td>Emotional stress</td>
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<td>Hot weather</td>
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<tr>
<td>Wind</td>
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<td>Heavy exercise</td>
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<td>Alcohol consumption</td>
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<td>Hot baths</td>
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<td>Cold weather</td>
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<td>Spicy foods</td>
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<td>Spicy foods</td>
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Table 2. Clinical subtypes of rosacea

<table>
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<th>Subtype</th>
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<tr>
<td>Erythematotelangiectatic rosacea (ETR)</td>
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<tr>
<td>Papulopustular rosacea (PPR)</td>
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<tr>
<td>Phymatous rosacea</td>
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<td>Ocular rosacea</td>
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Figure 2. Papulopustular rosacea is characterised by inflammatory papules and pustules; topical metronidazole and azelaic acid are beneficial, as are oral tetracyclines.
function of the skin and enhance tolerability of topical medications. Soothing moisturizers with a high water content can be helpful for symptomatic burning and flushing. Patients should also be advised that cosmetic camouflage advice is available.4

Patients with ocular rosacea should be advised on lid hygiene. Warm soaks and compresses are recommended along with twice-daily cleaning of the base of the lashes with baby shampoo or proprietary lid cleansers along with the removal of any crust. Artificial tears are advised for patients with dry eyes. Ocular symptoms will often improve with oral antibiotics. One study showed benefit from topical ciclosporin6 but this is an unlicensed use.

Facial redness is the commonest feature of rosacea and the most difficult aspect to treat. Topical and oral antibiotics offer limited benefit in treating the background erythema. Recently, however, the US Food and Drug Administration (FDA) has approved a topical alpha-2 adrenergic agent for the treatment of redness in rosacea and other similar agents are in development.6

Topical agents
Although there are numerous treatments available for rosacea there have been very few well-designed clinical trials.

A Cochrane review evaluated 58 randomised controlled trials of rosacea therapies. The two most commonly used topical agents metronidazole and azelaic acid (Finacea) were better than placebo in 6633 patients with moderately severe rosacea.7 In studies comparing the two there was no significant difference between the treatment groups in terms of patient-assessed outcomes.8

Both agents have been shown to reduce inflammatory lesions and perilesional erythema and possibly a reduction in background erythema. They are most beneficial in PPR.

Metronidazole 0.75 per cent cream or gel
Topical metronidazole has been used for decades to treat rosacea. Its mechanism of action is thought to be anti-inflammatory by reducing the release of reactive oxygen species from neutrophils. It is applied once to twice daily for 8 to 16 weeks. Topical metronidazole has also been shown to be effective in maintaining remission.9

Azelaic acid 15 per cent gel
Azelaic acid possesses anti-inflammatory actions that are believed to stem from suppressing neutrophil-derived reactive oxygen species. Azelaic gel applied once daily has been demonstrated to be as effective as twice daily, which is the generally recommended dosing schedule.10

Other topical therapies
Other topical antibiotics such as erythromycin and clindamycin, along with calcineurin inhibitors (tacrolimus, pimecrolimus), are sometimes used as second-line treatments but there are little data to support their use.

Brimonidine 0.33 per cent gel, recently approved by the FDA, is the first agent developed specifically to target the redness of rosacea. Clinical trials have shown significantly greater improvement in facial redness compared with the vehicle gel control. It is not yet available in the UK.

Oral agents
Tetracycline antibiotics have been used and been effective for decades in the treatment of PPR. Their benefit in rosacea is via an anti-inflammatory mechanism. Tetracyclines are known to have a host of anti-inflammatory properties and have been shown to indirectly inhibit cathelicidins by directly inhibiting matrix metalloproteinases (MMPs).11

Nonmicrobial doses of slow-release doxycycline 40mg (Effacea) have been shown to be as effective as 100mg (unlicensed indication) antimicrobial doses, supporting a primary anti-inflammatory rather than antimicrobial effect in rosacea.12 Lower-dose doxycycline has the advantage of avoiding the development of resistance as well as the phototoxicity seen at higher doses.

Other tetracyclines such as lymecycline 408mg daily and minocycline 100mg daily have the advantage over traditional oxytetracycline 500mg twice daily of a once-daily dosage and lower potential for interaction with dietary calcium.

Oral therapy is generally continued until inflammatory lesions clear or 12 weeks of therapy. As with topical therapy oral antibiotics are most effective in the papulopustular form of rosacea.

It is common practice to use both a topical preparation such as metronidazole or azelaic acid in combination with an antibiotic such as doxycycline to bring an acute flare under control. Once the inflammatory component responds the patient can be continued on topical treatment.

Other oral antibiotics
Although not commonly used, other oral antibiotics that have been used include erythromycin 250–500mg twice daily, amoxicillin 250–500 three times daily and metronidazole 200mg three times daily. Azithromycin 250mg three times weekly is also effective and has been used in refractory disease.
Isotretinoin
Isotretinoin is used in the treatment of severe and phymatous rosacea (unlicensed indications). It has been shown to reduce early rhinophyma and is useful for nodular inflamed disease. It is used in lower doses than to treat acne. Unfortunately rosacea tends to relapse once the treatment is stopped.

Laser and light therapies
Laser treatment is effective at reducing the redness and telangiectasia of rosacea. It is probably the most useful modality for treating ETR. Studies compared pulsed-dye laser to intense pulsed light and found both therapies to be effective, with no difference between the two.13 Telangiectasia can recur after some time.

The ablative CO₂ laser or erbium YAG laser can be used to treat rhinophyma/phymatous disease.

Surgical care
Surgical care is indicated for established rhinophyma. Surgeons use excision, the CO₂ laser, the cauterising scalpel or a combination of these.

Conclusion
Management strategies in rosacea need to address the multifactorial aetiology and varied clinical picture of the disease. Increased understanding of the aetiology and inflammatory mechanisms involved in rosacea should allow the development of more targeted therapy in the future.

It is important that patients are made aware from the outset of the chronic relapsing-remitting nature of rosacea and have realistic expectations of the outcome of treatment. Advice on lifestyle, trigger avoidance and appropriate skin care should underpin pharmacological therapy.

References

Declaration of interests
None to declare.

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CPD: Management of rosacea
Answer these questions online at Prescriber.co.uk and receive a certificate of completion for your CPD portfolio. Utilise the Learning into Practice form to record how your learning has contributed to your professional development.

For each section, one of the statements is false – which is it?

1. Rosacea is a common chronic inflammatory dermatitis that:
   a. may affect people of all skin types
   b. may be worsened by sun exposure
   c. is associated with increased expression of Toll-like receptor 2 in the skin
   d. usually presents before the age of 30

2. Rosacea is classified into four clinical subtypes, of which:
   a. PPR is the most common
   b. ETR is the most difficult to treat
   c. phymatous rosacea is characterised by thickening of skin with irregular surface nodularities
   d. ocular rosacea may be associated with intolerance of contact lenses

3. In the management of rosacea:
   a. all patients should use sunscreen
   b. metronidazole gel is not effective in patients with moderately severe rosacea
   c. azelaic gel applied once daily is as effective as twice daily
   d. moisturisers enhance the tolerability of topical medication

4. In the treatment of rosacea:
   a. azithromycin 250mg three times weekly has been used in refractory disease
   b. slow-release doxycycline 40mg is less effective than doxycycline 100mg
   c. isotretinoin is useful for nodular inflamed disease
   d. laser therapy is probably the most useful modality for treating ETR