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C. Diehl
Universitá Degli Studi Guglielmo Marconi, Rome, Italy

New Insights into Rosacea Part II. Treatment

Rosacea is a chronic skin disease which often tends to be underdiagnosed or misdiagnosed.

However, rosacea strongly impacts the quality of life of sufferers, both in their social and professional life and for this reason advice is sought from the dermatologist. Rosacea is a treatable, but not curable disease, which implies long term treatments in order to alleviate signs and symptoms and improve the skin appearance. Besides the treatment itself, education of the patient is compulsory, in order to teach the importance of sun protection, skin care and make up, but also avoidance of the well-known triggering factors. Regarding therapies, new options have recently appeared in our armamentarium which are described, along with the clinical evidences supporting them. They must be taken into account at the time of prescribing an adequate treatment to the patient, the prescription being primarily based on the clinical experience.

Key words

Rosacea, treatment, metronidazole, azelaic acid, retinoids, ivermectin, brimonidine.

In the first part of this work, we had described and discussed in detail the pathogenesis of rosacea and its different causative and triggering factors. There was also a reminder about the currently accepted classification of rosacea, which will be very helpful in the management and treatment of the disorder.

In clinical practice, rosacea tends to be underdiagnosed or misdiagnosed [1]. Doctors may not pre-emptively discuss rosacea with their patients, and studies have shown that only 10 % of patients actively seek professional care [2]. However, rosacea is known to affect both social and professional lives and can lead to psychosocial problems – surveys have reported that 41 % of rosacea sufferers avoid social and public contact and 76 % experience low self-esteem [2]. In addition, rosacea sufferers also have to contend with commonly associated stigmas: facial erythema incorrectly signifying alcohol abuse or an inability to cope with stress [2]; and the presence of papules and pustules being mistaken for a lack of personal hygiene [3]. This low proportion of patients with rosacea seeking medical advice suggests that besides the great majority of rosacea sufferers who do not intend to manage it, some of them are reporting to their GP, their pharmacist or even worse their relatives and this may explain that often, rosacea is mismanaged and may worsen, in particular when the therapy is based on corticosteroids which will lead to the occurrence of steroid rosacea, whose treatment is difficult.

Aims of therapy

Rosacea is treatable, but presently not a curable disease. Key goals of treatment are to alleviate signs and symptoms and improve appearance, delay or prevent development of more advanced stages of the condition and to sustain remission [4]. One of the challenges in treating rosacea lies in the need to alleviate the range of symptoms that can present simultaneously, such as facial erythema and papules and pustules. An approach involving the use of concomitant therapies for the treatment of different symptoms would help attain the optimum results for the patient with a range of symptoms of rosacea.

The ROSacea International Expert (ROSIE) consensus group works on the premise that current treatment of rosacea is not causal but symptomatic and, therefore, signs and symptoms should be at the forefront of therapeutic decision making [4]. This concept was issued by a group of European specialists in rosacea, and features the current vision of rosacea treatment shared by most of European dermatologists. This concept differs from the therapeutic approach based on the classification systems, which identifies the rosacea stage or subtype

and then makes assumptions as to what treatment to choose, which is more widespread among American practitioners. For this reason, we shall study separately both options of treatment in this review.

European concept of treatment of rosacea

This was stated by the ROSacea International Expert (ROSIE) consensus group [4].

In this concept, the objectives of therapy are:

1) to alleviate signs and symptoms such as skin reddening or irritation and reduce papules and pustules;
2) to delay or prevent development from the milder to the more severe stages of the condition;
3) to facilitate remission and avoid exacerbations;
4) to maintain the skin in as good a condition as possible;
5) to improve patient's quality of life.

An interesting new idea is the triad of rosacea care which provides a comprehensive approach to address all the needs of rosacea patients, then undermining the approach consisting in addressing separately the symptoms of the disease.

This triad is based on Education + Skin care + Treatment; these three components being complementary and compulsory in the establishment of a treatment aimed to bring satisfaction to our patients.

First, **patient education** is a vital point in the treatment of rosacea. Oral information, but also when possible written information should be provided to our patients, bringing information about the importance of skin care, make-up and the psychological aspects of rosacea, Last but not least, patients must be informed about the necessity of avoiding triggering factors such as sun-exposure, extreme temperatures, stress, intake of alcohol, hot drinks and spicy food.

Skin care is another cornerstone in the successful treatment of rosacea. Provision of instructions on skin care and cosmetics, in particular in female rosacea patients, can help in improving their quality of life and reducing the cosmetic mismanagement which could worsen the symptoms. It is primordial to insist on that the use of sun protectors by rosacea patients is compulsory. Unfortunately, these patients have very often sensitive skin, which may cause some degree of intolerance to chemical filters. On the contrary, physical sunscreens like zinc oxide or titanium dioxide are usually well accepted and should be recommended in priority to rosacea patients.

An overview of **therapeutic approach** based on the signs and symptoms of rosacea is provided in Table. We shall discuss in detail each of the topical and systemic medication options.

Topical agents provide the mainstay of treatment for many patients with rosacea. They are usually used alone in patients suffering grade I (erythematotelangiectatic rosacea — ETR) and more often combined with systemic treatment in grade II (papulopustular rosacea — PPR). In EU, the three primary drugs having obtained approval for the topical treatment of rosacea are metronidazole, azelaic acid and sulfacetamide-sulphur. Other therapies are also successfully used, but have not gained approval at this stage.

Topical metronidazole

Metronidazole (MTZ) is an antibiotic and antiprotozoal nitroimidazole component. It also appears having anti-inflammatory and antioxidant activity. MTZ is usually presented as 0.75 % cream or 1 % gel. The efficacy of MTZ on moderate-to-severe rosacea has been assessed by various studies [5—7]. It reduces papules and pustules and sometimes alleviates erythema, but has little effect on telangiectasis. A meta-analysis of efficacy rates for different metronidazole formulations demonstrated that there were no significant differences between concentrations of 0.75 % and 1 %, cream, gel and lotion vehicles or between once or twice daily application [8]. The overall safety and tolerability profile of MTZ is favourable, with most adverse events related to local tolerability reactions.

Azelaic acid

Azelaic acid (AA) is a dicarboxylic acid with antimicrobial, anti-inflammatory, and antikeratinizing properties [9]. Two double-blind randomized controlled studies involving 664 patients demonstrated that a gel formulation containing 15 % azelaic acid was more effective than vehicle in the reduction of both papulopustular lesions and erythema [10] which was confirmed by Cochrane analysis [11]. A few well-controlled studies comparing MTZ and AA in participants with PPR demonstrate comparable efficacy in the reduction of inflammatory lesions, with one study of AA gel 15 % twice daily versus MTZ gel 0.75 % twice daily noting superior reduction in facial erythema in the AA treatment group beyond 8 weeks of use [12—13]. AA has a favourable tolerability profile as local skin reactions, such as facial burning, stinging, and pruritus, occur but are mostly rated as mild to moderate in intensity [4].

Sulfacetamide 10 % + Sulphur 5 %

This combination drug, available in lotion, cream or gel was initially used in the treatment of acne. The sulfacetamide has antibacterial properties, and the sulphur component confers antifungal, antidemodectic and keratolytic effects [4]. Various studies proved the efficacy of topical sodium sulfacetamide

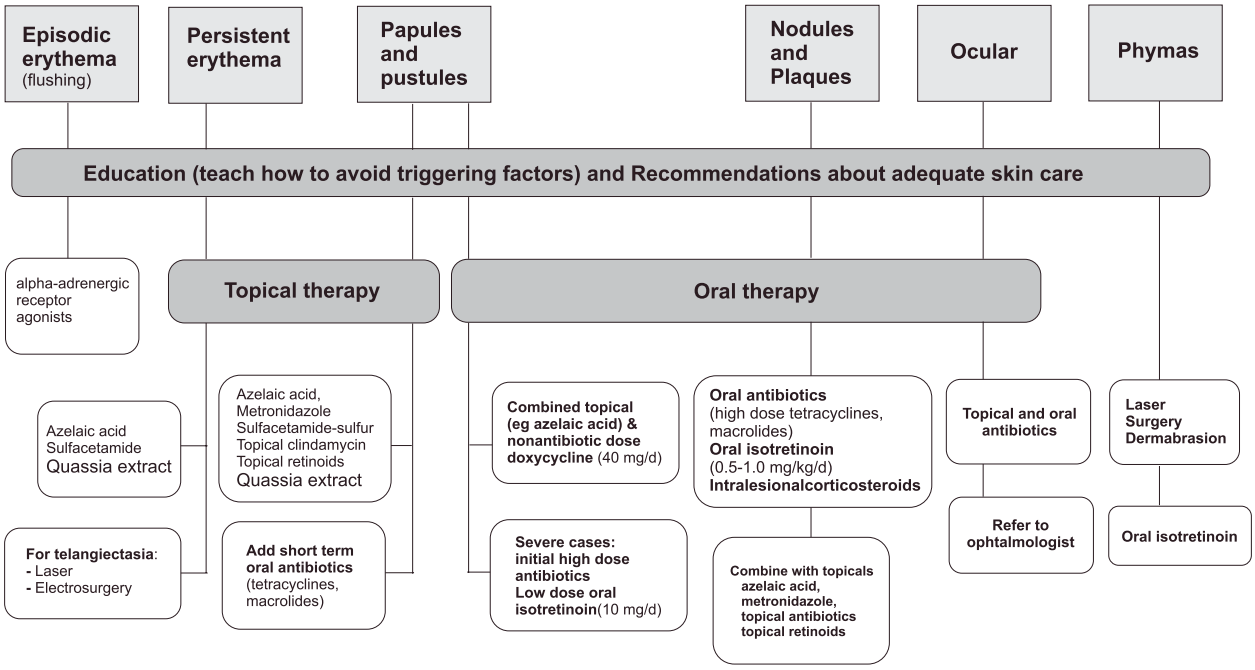

Table. **Algorithms of treatment of rosacea based on signs and symptoms**

and sulphur in rosacea [14—16]. Two studies comparing the sodium sulfacetamide 10 % + sulphur 5 % with metronidazole 0.75 % gel [17—18] showed a greater percentage of reduction in inflammatory lesions and a greater proportion of success in global improvement with the combination than with MTZ. Tolerance appears to be satisfactory.

Topical antibiotics

A variety of antibiotics, macrolides or macrolides analogues, are used as topical treatment of rosacea. They include erythromycin, clindamycin and azithromycin. Good results were reported in rosacea with 2 % erythromycin lotion [19]. Topical clindamycin 1 % features a lotion or a gel. Compared with oral tetracycline (1000 mg/day for 3 weeks, then 500 mg/day), clindamycin 1 % lotion produced similar clinical results to oral tetracycline [20]. Combination of clindamycin 1 % and benzoyl peroxide 5 %, a recognized treatment for acne, was found to be effective in inflammatory lesions and erythema of rosacea [21] and this combination therapy was shown to be significantly more effective than each ingredient alone [22]. Azithromycin in a 2 % topical solution was assessed with good results on inflammatory lesions of rosacea, its efficacy being ranged as comparable with topical erythromycin [23].

Topical retinoids

Topical retinoids, including tretinoin, tazarotene and adapalene are used in some countries for treating rosacea but there is limited evidence to support their use. 0.025 % tretinoin cream appeared to be beneficial in treating severe or recalcitrant rosacea [24]. However, topical retinoids aggravate the underlying vascular disease and are often considered controversial for rosacea because they are potentially irritant and therefore can cause problems in patients with sensitive skin [4].

Topical corticosteroids

Topical corticocosteroids can be useful for short-term treatment of severe inflammatory rosacea but long-term use must be avoided as the clinical problem will be aggravated with side-effects from prolonged use and potential exacerbation by steroid-induced rosacea can occur [25]. Corticosteroid nasal sprays have been reported as a possible trigger for rosacea [26].

Other topical treatments

Permethrin, an insecticide, acaricide, and insect repellent is a first-line treatment for scabies. Permethrin 5 % cream was found to be a safe alternative for the topical treatment of papulopustular rosacea, superior to metronidazole 0.75 % gel and placebo in decreasing *Demodex folliculorum*, and as effective as metronidazole 0.75 % gel in treating erythema and papules [27]. There have been several case reports about use of topical permethrin in rosacea, usually in combination with or after oral ivermectin therapy. Oral ivermectin plus topical permethrin were found to be efficient both in a patient with immune compromise and in immunocompetent patient with

PPR [28, 29]. Interestingly, both of them were refractory to other therapies.

Calcineurin inhibitors (tacrolimus and pimecrolimus) were also assessed in the treatment of rosacea.

Use of tacrolimus appears to be deceptive, as in a group of 24 patients with ETR and PPR treated over 12 weeks with 0.1 % tacrolimus, there was no decrease in the number of papules/pustules, but significant improvement in erythema [30]. Meanwhile, tacrolimus should be employed carefully in this indication, as various severe side effects were described, such as induction of rosacea-like dermatitis [31—33] and granulomatous rosacea [34, 35]. There are more reports about the use of pimecrolimus in rosacea. Pimecrolimus 1% cream was shown to be an effective and well-tolerated treatment for patients with mild to moderate inflammatory rosacea [36] even when the disease was recalcitrant to conventional treatments [37]. On the contrary, it was shown that pimecrolimus 1 % cream was not more effective than the treatment with placebo in PPR [38, 39] in contradiction with another study displaying results as satisfactory as with MTZ 1 % cream [40]. A few cases of granulomatous rosacea successfully treated with pimecrolimus 1 % cream were reported [41, 42].

Treatment with pimecrolimus 1% cream appears to be also efficient in steroid-induced rosacea [43, 44]. As for tacrolimus, severe side effects were described with pimecrolimus, such as rosaceiform dermatitis [45—47] or rosacea-like demodicidosis [48, 49].

Another promising opportunity comes with the use of topical *Quassia amara* extract. In a single-centre, open-label study, a group of 30 patients with rosacea of variable severity were treated with 4 % *Quassia amara* extract topical gel for 6 weeks. Reportedly, *Q. amara* possesses antiparasitic and anti-inflammatory properties that have the capability to decrease the inflammatory response with few complications. Efficacy comparable with that of first-line topical treatments like azelaic acid and metronidazole was observed after *Q. amara* treatment, with superb tolerability [50].

Emerging topical therapies: Ivermectin and Brimonidine

Ivermectin is derived from avermectin, a class of broadspectrum anti-parasitic agents isolated from the fermentation of *Streptomyces avermitilis*. Ivermectin possesses both antiparasitic and anti-inflammatory properties and has been shown to reduce the number of *Demodex* mites in demodicidosis and blepharitis and to inhibit the production of lipopolysaccharide inflammatory cytokines, such as tumor necrosis factor-alpha and interleukin (IL)-1b, while upregulating the production of the anti-inflammatory cytokine IL-10 [51]. For the first time in 2014 topical ivermectin 1 % cream was assessed vs. its vehicle and shown to be effective and safe in treating inflammatory lesions of papulopustular rosacea [52]. Further, in a blinded study, it was found that Ivermectin 1 % cream was significantly superior to MTZ 0.75 % cream regarding percentage reduction of inflammatory lesions in subjects with moderate to severe PPR [53]. In addition, investigating remission over a 36-week extension period in patients with moderate to severe PPR successfully treated with 16 weeks' treatment with ivermectin 1 % cream once daily or MTZ 0.75 % cream twice daily, the results of the relapse study showed that an initial successful treatment with ivermectin 1 % cream significantly extended remission of rosacea compared with initial treatment with MTZ 0.75 % cream BID following treatment cessation [54].

Brimonidine is an α-2 adrenergic receptor agonist, and works by reversing skin vasodilation. Hence topical brimonidine will be exclusively used on the erythematous symptom of rosacea. In a vehicle-controlled study, once-daily brimonidine tartrate (BT) gel 0.5 % was well tolerated and providing significantly greater efficacy than vehicle gel for the treatment of moderate to severe erythema of rosacea [55]. Effect of topical BT gel 0.5 % on erythema severity was observed after the first application and the durability of the effect was maintained until the end of another study at month 12, with no tachyphylaxis observed [56]. The main characteristic of BT gel is that the effect is reached after half an hour, but is only temporary, lasting until 12 hours. One disadvantage is that the use of the product tends to bring a very pale, almost cadaveric skin tone during this period. Use of BT in routine clinical practice has yielded new insights that elaborate on the findings from clinical trials. For example, real-world use has shown that a percentage of patients (approximately 10 to 20 %) treated with BT experience a worsening of erythema that has been called «rebound» [57]. Flushing and erythema are the most commonly reported adverse events, occurring in a total of 5.4 percent of subjects in the Phase 3 studies and in 15.4 percent in the long-term study. Most adverse events are mild or moderate in severity, transient, and intermittent. Adverse events usually occur early in treatment, and duration is short-lived in the majority of cases [58].

Systemic therapies

Oral tetracycline (tetracycline hydrochloride) and its second-generation derivatives doxycycline and minocycline have for years been the mainstay in

systemic rosacea treatment. Oral antibiotics were used assuming that rosacea was caused by microbial infection. Although this has now been proven not to be the case, the benefits observed with antibiotic treatment have led to its continued use [59].

Tetracyclines are known to modulate the inflammatory response by down-regulating the production of pro-inflammatory cytokines such as IL-1 and TNF-a and the production of reactive oxygen species, which could explain their efficacy in the treatment of rosacea [60]. Data pooled from three studies of oral tetracycline vs. placebo involving 152 participants showed that, according to physicians' assessment, tetracycline was effective [4]. Usually doses were administered at levels consistent with antibiotic activity, i. e. 100–200 mg/day for doxycycline and 50–100 mg/day for minocycline. This has raised concerns about the development of antibiotic resistance in potential pathogenic bacteria.

More recently, a low dose 40 mg doxycycline preparation has been introduced, which contains 30 mg immediate-release and 10 mg delayed-release doxycycline [4]. At this anti-inflammatory dose, the doxycycline preparation has no antibiotic activity and consequently does not lead to the development of antibiotic resistant organisms [61]. Two randomized phase III clinical trials evaluating anti-inflammatory dose doxycycline (40-mg) administered once daily for treatment of PPR showed that this therapy was effective in decreasing the number of inflammatory lesion counts [62]. No additional improvement in rosacea symptoms is achieved with oral doxycycline 100 mg once daily (usual antibacterial dosage) compared with 40 mg [63].

Macrolide antibiotics including erythromycin, clarithromycin and azithromycin, as well as metronidazole, have all been used for systemic treatment of rosacea. Disadvantages of these treatments include gastrointestinal side-effects and the requirement of alcohol avoidance in the case of metronidazole.

Oral isotretinoin is anti-inflammatory and can be effective in treating rosacea but its serious side-effects in pregnancy preclude widespread prescribing.

American concept of treatment of rosacea

The therapeutic approach is slightly different and based on the classification systems, which identify the rosacea stage or subtype and then make assumptions as to what treatment to choose. Overall, treatment methods are very similar between Europe and America and also worldwide even though there are slight differentiations as a result of the fact that some products are only available in certain countries.

The most recent guidelines have been published in 2013 by the American Acne and Rosacea Society, encompassing topical but also systemic agents [64, 65].

Of course, these recommendations are highlighting topical and systemic agents approved by the US Food and Drug Administration (FDA) for the treatment of rosacea.

Topical therapies approved by US FDA

MTZ 0.75 % gel, cream, and lotion (twice-daily application); MTZ 1 % gel and cream (once-daily application); and AA 15 % gel (twice-daily application) are FDA approved for the treatment of inflammatory lesions of rosacea in patients with PPR.

Brimonidine tartrate 0.33 % gel was approved by the US FDA in August 2013 and by Health Canada in February 2014, and is the latest addition to the treatment armamentarium and the first topical agent approved for the treatment of facial erythema of rosacea.

All other treatments previously mentioned are not officially approved in this indication.

Systemic therapies approved by US FDA

The only oral agent that has been formally submitted for approval by the US Food and Drug Administration (FDA) for the treatment of inflammatory lesions of rosacea is a modified-release doxycycline capsule (40 mg once daily), which was approved in 2006.

Conclusion

Therapeutic interventions have been breaking new ground along with new technology, patient education, psychological evaluation and the use of dermo-cosmetics. Rosacea is a common, troublesome and sometimes difficult-to manage condition, affecting a large number of sufferers and requiring long-term treatment. Treatment must rely overall on clinical experience. The aims of treatment for rosacea are to reduce symptoms such as facial flushing and telangiectasias and eruption of papules and pustules, to prevent or delay worsening from milder to more severe manifestations of the condition as well as to maintain remission. By improving the physical appearance of the skin, the disabling psychological and social consequences of the condition can be relieved, and patients' quality of life and confidence improved. The chronic nature of rosacea, and the need for lifelong treatment, require chosen therapies to be effective, safe and well tolerated.

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К. Діл

Universitá Degli Studi Guglielmo Marconi, Rome, Italy

Нові погляди на розацеа Частина 2. Лікування

Розацеа — це хронічне захворювання шкіри, яке досить тяжко правильно діагностувати.

Розацеа суттєво впливає на якість життя хворих як у соціальній, так і у професійній сферах. Лікування потребує консультації дерматолога. Розацеа піддається лікуванню, але не виліковується повністю. Полегшення симптомів і поліпшення зовнішнього вигляду шкіри вимагає тривалого періоду лікування. Крім лікування, пацієнта обов'язково слід навчити захищати шкіру від сонячного проміння, правильно доглядати за нею та користуватися захисною косметикою, а також уникати чинників, які провокують загострення хвороби. Що стосується лікування, то останнім часом в нашому арсеналі з'явилися нові можливості, які ми описуємо разом із клінічними доказами на їх підтримку. Їх необхідно взяти до уваги, призначаючи лікування, яке насамперед повинно базуватися на клінічному досвіді.

Ключові слова: розацеа, лікування, метронідазол, азелаїнова кислота, ретиноїди, івермектин, бримонідин.

К. Дил
Universitá Degli Studi Guglielmo Marconi, Rome, Italy

Новый взгляд на розацеа
Часть 2. Лечение

Розацеа — это хроническое заболевание кожи, которое достаточно трудно правильно диагностировать.

Розацеа существенно влияет на качество жизни больных как в социальной, так и в профессиональной сферах. Лечение требует консультации дерматолога. Розацеа поддается лечению, но не излечивается полностью. Облегчение симптомов и улучшение внешнего вида кожи требуют длительного периода лечения. Помимо лечения, пациента обязательно следует научить защищать кожу от солнечных лучей, правильно ухаживать за ней и пользоваться защитной косметикой, а также избегать факторов, которые провоцируют обострение болезни. Что касается лечения, то в последнее время в нашем арсенале появились новые возможности, которые мы описываем вместе с клиническими доказательствами в их поддержку. Их необходимо принять во внимание, назначая лечение, которое прежде всего должно базироваться на клиническом опыте.

Ключевые слова: розацеа, лечение, метронидазол, азелаинова кислота, ретиноиды, ивермектин, бримонидин.

Дані про автора:

Dr. Christian Diehl, Department of Dermatology, Universitá Degli Studi Guglielmo Marconi
Via Plinio, 44, 00193, Rome, Italy
E-mail: chdiehl@hotmail.com