ADVANCES IN ROSACEA THERAPY

A REVIEW OF AVAILABLE THERAPIES.

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Rosacea has several different appearances. There are four well-defined subtypes of rosacea:

1. erythemato-telangiectatic
2. inflammatory
3. phymatous
4. ocular

The most typical appearance that many of our patients have is subtype 1 (erythematotelangiectatic). This facial redness is one of the symptoms that bothers patients the most, and our greatest challenge in the area of rosacea is to try to develop therapies that can target this type of redness.

This article will cover several therapies for rosacea, provide data on how the therapies rate in clinical trials, discuss potential side effects and provide other general information about rosacea. This article will review new information regarding oral, topical and physical therapies for rosacea, as well as over-the-counter products that can help with redness. And, while flushing is one of the most difficult aspects of rosacea to control, this article will not focus on it because no effective treatment exists for flushing.

THERAPEUTIC APPROACH

One of the first things to discuss with rosacea patients is what constitutes a good skincare regimen. Discuss sun protection, avoidance of trigger factors and proper skin and eye care. Explain the rationale behind the choices for different therapies. What's the advantage of an oral therapy compared to a topical therapy? Should they both be used together? When should a patient use oral therapy? When should a patient use the topical therapy? These are questions that patients have.

ORAL THERAPIES

Oral therapies target the inflammatory lesions and ocular rosacea, flushing, and the very extreme or recalcitrant traces of rosacea. For the extreme or recalcitrant rosacea, isotretinoin can be used. However, in my experience, patients seem to do well while taking isotretinoin, but unlike with acne, when patients stop the isotretinoin, the rosacea comes back and it tends to be just as bad.

Tetracyclines can target inflammatory activity. Tetracyclines can downregulate the expression of proinflammatory cytokines. They can inhibit the production of arachidonic acid metabolites, which lead to inflammation. They can inhibit angiogenesis, reactive oxygen species, neutrophil chemotaxis and matrix metalloproteinases.

This newest product in this category is an anti-inflammatory dose doxycycline in a 40-mg controlled release formulation (Oracea). It's formulated with 30 mg of doxycycline in an immediate release, and then 10 mg that's released over time. This is FDA approved as a once-daily treatment of rosacea, and at this dose it does not kill bacteria.

With regular doxycycline 50 mg twice a day, you exceed the level needed to kill bacteria, which would, therefore, raise concerns about bacterial resistance. With Oracea's formulation, it never reaches that antimicrobial level, so it doesn't kill the bacteria, yet it still has the beneficial anti-inflammatory properties of tetracycline.

There were two Phase III pivotal trials in patients with rosacea for Oracea.[1] They were 16-week studies with 537 patients. In the first study, the reduction in inflammatory lesions was about 60%. In the second study there was a reduction in inflammatory lesions on the order of 50%.

In terms of safety for Oracea, there was no antimicrobial activity. There was no evidence of adverse events. One of the advantages to using the sub-antimicrobial dose of doxycycline is that patients don't get the side effects associated with full dose antibiotics. The contraindications and warnings[2] are similar to those found in any tetracycline, such as hypersensitivity and risk of tooth discoloration.

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It's important to note that for almost all rosacea treatments, the reduction rates in inflammatory lesions are very similar. Reduction rates range from 48% to 55% or 60%. Obviously, there are differences among therapies and differences among our patients — it's a matter of finding the right treatment regimen that works for a particular patient.

TOPICAL THERAPIES

The primary topical therapies are metronidazole (MetroGel, Noritate), azelaic acid (Finacea) and sulfacetamide/sulfur products (Avar, Clenia, Plexion, Rosac, Rosanil, Rosula, Sulfacet-R, Klaron and Ovace).[3] These therapies have been studied and approved for use in rosacea. Secondary topical therapies that are used in rosacea, but that have not been as highly studied, include clindamycin, erythromycin and benzoyl peroxide. Other agents, tretinoin and the topical calcineurin inhibitors, have been used on a case-by-case basis.

Metronidazole is available as 1% gel or cream and also as a 0.75% generic formulation. The 1% metronidazole gel (MetroGel) is in a vehicle containing 92% water and HAS-3 (a mixture of three hyrdo-solubilizing agents: niacinamide, betadex and a low concentration of propylene glycol). A comparative *in vitro* study compared the penetration of the 1% gel to the 1% cream.[4] The study found that there was much more of the gel contained within the skin compared to the cream. In terms of reduction in inflammatory lesions, after 10 weeks there was about a 67% reduction. The global assessment or percentage of patients assessed with a score of clear, mild or almost clear after the 10 weeks included about 73% of patients.

The 1% gel is indicated for the inflammatory lesions of rosacea. Burning, skin irritation, dryness, transient redness, metallic taste, tingling, numbness of extremities and nausea are side effects associated with topical use of metronidazole.

Azelaic acid 15% (Finacea) was one of the first products that was re-formulated from a cream to a gel. It was formulated as a stable aqueous, polyacrylic-acid-based gel. Several studies showed a higher percentage of dissolved azelaic acid in gel (25%) versus cream (3%), for improved drug release and bioavailability. A hairless mouse study showed there is also a higher absorption into skin (25.3%) with the gel as compared to the cream (3.4%).

Efficacy and safety for azelaic acid 15% to treat moderate papulopustular rosacea was evaluated in three Phase III, multicenter, double-blind, randomized studies (n=955).[6,7] Data from the Phase III trials show that the reduction in inflammatory lesions was about 54% after 12 weeks of treatment. In one study,[6] the facial erythema of the patients was also rated. The percentage of patients who had improvement in erythema was statistically significantly different from the placebo group with 45% of patients in the azelaic acid group showing improvement in erythema compared to 28% in the placebo group ($p<0.0001$). With azelaic acid 15% gel, there was also significant improvement in inflammatory lesions, erythema and in the global severity scale.

Side effects included some burning, stinging and tingling, as well as itching. Most of these effects were mild and transient and did not interfere with the ongoing treatment. There was a review of the use of azelaic acid in the treatment of rosacea published in *The Archives of Dermatology* in August of 2006.[8]

PHYSICAL THERAPIES

The telangiectasia of rosacea for most patients are permanent. They're caused by sun damage, alterations in collagen and a variety of factors. Many treatments have been tried for telangiectasia — oral and topical therapy are ineffective, and it's the laser and light therapies that seem to be the most helpful.

The monochromatic light sources that have been used include the KTP laser, pulsed dye laser and the CO_2 laser. The KTP and pulsed dye lasers are effective for telangiectasia and erythema. The CO_2 laser has been used in combination with a variety of other treatments such as the cauterizing scalpel to try to re-sculpt the nose. Polychromatic intense pulsed light has also been used for telangiectasia and erythema.

One study evaluated the effects of a pulsed dye laser in 16 patients with erythematotelangiectatic rosacea.[9] After two treatments at 8-week intervals, patients showed improvement in their symptoms, quality of life scores and erythema. In another study that also evaluated pulsed dye laser therapy, 10 patients with papulopustular rosacea with erythema and telangiectasia underwent half-face treatments.[10] They had an average of 2.4 treatments until symptoms resolved. There was a mixed response in terms of improvement of papules and pustules. These physical therapies seem to be more effective at targeting telangiectasia and erythema, while papules and pustules are better targeted by the topical and oral medical therapies discussed.

In terms of intense pulsed light therapy, there is a need for more controlled trials for evaluating this treatment for rosacea. In a 2003 study,[11] four patients with erythema and telangiectasia underwent five treatments with Photoderm VL 15 nm-light at 3-week intervals. Patients were assessed at baseline and 1 month following the last treatment. Results showed there was a 30% decrease in blood flow using Doppler, a 29% decrease in the area of the cheek involved with telangiectasia and a 21% decrease in erythema using computer analysis of photographs.

Therapies for rhinophyma, an area that can make a big difference in patients' appearances, include cold steel excision, CO_2 laser, the cauterizing scalpel and a combination of these treatments.

OVER-THE-COUNTER PRODUCTS

In the past year, a significant number of advances in over-the-counter therapies have emerged. Some moisturizers, sunscreens and cleansing products now contain natural ingredients that *in vitro* studies and small clinical studies have suggested might help to improve erythema in rosacea patients, and probably in acne patients as well. One such ingredient is Licochalcone, which is found in the Eucerin brand of the anti-redness products. It is a licorice root extract that inhibits lipoxygenase, which is in the arachidonic acid pathway. The products include claims for reduction of sebum production, sun protection and reduction of facial redness. Although it is not known how they were all tested, it is known that this ingredient can inhibit this particular enzyme and may then reduce erythema.

The Aveeno and Purpose anti-redness lines of skin care contain feverfew. Feverfew is an allergen, but for these products feverfew has been modified so that it's not antigenic, and it seems to work well in these over-the-counter lines for reducing redness.

MANY OPTIONS FOR ROSACEA

In summary, the medical treatments work best against the inflammatory lesions. The medical treatments also may help with erythema, though results are not consistent and it's difficult to predict which patients will see improvement in erythema. The physical modalities seem to be the most effective for the telangiectasia and for persistent erythema. Lifestyle modification can also help. Patients need to avoid trigger factors, and there are simple everyday modifications patients can make to improve their conditions. For example, a lot of people with rosacea may be blow-drying their hair, and the heat of the hair dryer can be irritating and lead to flare. Air-drying hair could help avoid a flare. Cosmetics, such as green-tinted foundations and makeup, help to mask the erythema.

There are many options for rosacea, but there is no one right answer, there is no one magic medication. Working with patients to develop regimens they can adhere to and being willing to adjust those regimens as needed will make a big difference in successful patient outcomes. ■

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