

AN EDUCATIONAL SUPPLEMENT

DermatologyTimes®

CLINICAL INSIGHTS THAT EXPAND EXPERTISE AND ADVANCE PRACTICE

BEST
PRACTICES
IN THE
TREATMENT
OF
ROSACEA



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FACULTY & DISCLOSURES

PANELISTS



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ROSACEA is a common skin condition that often manifests as redness and flushing, as well as pimples and pustules on the face. Some patients may have evidence of dilated blood vessels near the surface of the skin (telangiectasia) or thickening of the skin, especially around the nose (rhinophyma).

BEST PRACTICES IN THE TREATMENT OF ROSACEA

Recent rosacea research has focused on developing a better understanding about the pathophysiology of rosacea, as well as therapeutic agents and drug combinations that may be effective in treatment-specific rosacea symptoms.

For this supplement, *Dermatology Times* invited a group of experts in rosacea to discuss some of the latest findings and their potential impact on day-to-day clinical practice for practicing dermatologists.

PATHOPHYSIOLOGY OF ROSACEA

Dermatology Times: What, if any, new information has recently come to light about the pathophysiology of rosacea that is important for dermatologists to know?

Dr. James Q. Del Rosso: While the dermatology community has made progress in understanding different components of the pathophysiology of rosacea, I think it's fair to say that there is a lot we still don't understand.

There appear to be different components that drive the development of rosacea. There is neurovascular dysregulation, which predisposes an individual to acute vasodilation or flushing, along with the burning, stinging, and the

diffuse erythema.¹ And then there is the progressive fixed dilatation of the blood vessels that leads to telangiectasias and background erythema.² The other major component of the pathophysiology of rosacea is augmented immune detection/response, which triggers pathways such as the cathelicidin cascade, which causes both erythema and, in some patients, papules and pustules.

I think about the pathophysiology of rosacea in much the same way as I learned to think about the pathophysiology of acne over the years. We accept the fact that there are different components of the pathophysiology of acne that are addressed with different treatments, and we don't typically treat an acne patient with just a single therapy. But for some reason, we haven't gotten to that point with rosacea. Many dermatologists do not look at the rosacea patient and say, "OK, what's happening from a pathophysiologic perspective that can be addressed with an individual treatment?" We need to begin correlating different signs and symptoms with different treatments instead of that "one for all" or subtype approach.

Dr. Neal Bhatia: There has been a lot of recent discussion about the possible connection between rosacea and *Helicobacter pylori* and other concomitant parasites in the gut that mimic or resemble a hypersensitivity response similar to what is proposed about

Demodex.^{3,4} I don't think we yet know if there is a symptomatic gastrointestinal (GI) contribution that leads to the development of rosacea, but there are studies currently under way that may clear up some of the primary questions.⁵

Personally, I am not a big believer in the link between GI parasites and the development of rosacea, though there are some dermatologists who will try to reduce a rosacea patient's gut flora load during their treatment. Hopefully, we'll know more about whether this is a reasonable approach to treatment in the near future.

Dermatology Times: What is known about any genetic predisposing factors to the development of rosacea?

Dr. Hilary Baldwin: We just finished a study at the Twins Days Festival in Twinsburg, Ohio, which is an annual meeting of approximately 2500 biologic twins. We looked at 65 twin sets whom we identified with mild-to-moderate rosacea—only 1 twin set had severe disease—and while the results of our study have not yet been published, I can report that there was a great deal of symptom concordance between the identical twin sets, even among twins who had lived apart for 5 or even 10 years.⁶ Our results are in line with what a similar study from Case Western Reserve concluded in 2015, showing that about half of the contribution to the development of rosacea

comes from genetics and the other half comes from the environment through things such as ultraviolet exposure, alcohol, and smoking.⁷

These results have me convinced that there is a genetic influence that drives the development of rosacea.

Dr. Del Rosso: At a recent meeting of the Rosacea International Study Group, Dr. Martin Schaller of the University of Tübingen in Germany showed photographs of mothers and children who both had very similar clinical presentations of rosacea.⁸ It's not often that we hear about a familial link to rosacea, and I suspect few of us consistently ask our patients about it.

Dermatology Times: What are the major clinical features of rosacea? Which do you find to be most burdensome from a patient perspective?

Dr. Guy Webster: There are many ways to think about rosacea. You can think of it as several different subtypes of the same disease, or you can think about it as a general predisposition that may have 1 or more of the subtypes. In general, you've got the red face, you've got the pimples, and you've got ocular rosacea that includes styes and blepharitis where there has been an overgrowth of sebaceous glands.

What bothers the patient most? It varies, but in general, the pimples seem to be most bothersome, although some

patients—especially women—with erythema can be made to feel really self-conscious and uncomfortable.

Dr. Baldwin: While my experience would lead me to agree with Dr. Webster, there was a study published in June 2017 with which both Dr. Del Rosso and I were involved that found otherwise. In the study, we collected patient surveys that explored a variety of questions and found that it was patients' erythema and not their pimples that were the most bothersome reported aspect of rosacea.⁹

The bottom line, however, is that the most bothersome feature of rosacea is whatever the patient has. A gentleman who comes in with a great deal of rhinophyma but with none of the other aspects of rosacea is going to be bothered by rhinophyma the most. Clearly, it's in the eyes of the possessor.

Dermatology Times: How, if at all, are you utilizing rosacea phenotyping during the diagnostic process? How is the grouping of rosacea patients by phenotype different than grouping by subtype?

Dr. Bhatia: When I see a new patient with suspected rosacea, my first order of business is to confirm the diagnosis. These days, you have so many people with static erythema or structural telangiectasias who were told they have rosacea by their neighbor, by "Dr. Google," or by the guy at the

"These days, you have so many people with static erythema or structural telangiectasias who were told they have rosacea by their neighbor, by "Dr. Google," or by the guy at the bar. They come in having already made up their mind that they have rosacea, and my number 1 charge is to convince them that they either have it or they don't."

bar. They come in having already made up their mind that they have rosacea, and my number 1 charge is to convince them that they either have it or they don't. That can be a little daunting without a clear family and medical history.

Assuming that the diagnosis of rosacea is eventually confirmed, then it becomes important to stratify them based on their symptoms: Are they papular, are they more erythematous, or are they a combination of both? That then will help guide treatment.

Dr. Baldwin: When a patient walks into my office, I take a good deal of time looking at the various

components of their condition, primarily because I will be treating them based on the pathophysiology of their unique constellation of signs and symptoms. I also think it's important to have the patient hold up a mirror so that I can point out to them the many signs of the disease that they may not have noticed. This allows me to talk to the patient about which signs and symptoms we're able to treat, which we're not able to treat, and how we might develop an overall treatment plan.

Dermatology Times: Does the presence of inflammatory papules and pustules as a primary

presenting feature alone typically signify the presence of rosacea? What about centrofacial erythema?

Dr. Webster: There's a threshold for every symptom beneath which you don't have disease. To some degree, that's cultural. If you walk around in Dublin, Ireland, you'll see that almost everyone has a little bit of rosacea. When you get to the point where there's blushing that the patient notices and they have some fixed erythema, that's probably the bottom end of the rosacea spectrum in my book. And while I can make a formal diagnosis based on pimples with proper morphology and location alone, there are usually pimples along with erythema.

Dermatology Times: Which features of rosacea are most difficult for providers to successfully treat?

Dr. Linda Stein-Gold: As has been mentioned previously, symptom control really requires a multimodal approach for a lot of our patients, because we have to look at each of the aspects of their disease.

In today's environment, we're very fortunate in that we have a lot more in our toolbox than we had several years ago, and I think we have agents that are quite effective in getting a patient's papules and pustules under control fairly rapidly. In addition, we're now able to get some of a

patient's background erythema under control with topical treatment. Probably the thing that's going to require the most skill to treat is rhinophyma, because it often requires a surgical intervention.

Dermatology Times: How do you determine if a patient should be classified as having mild, moderate, or severe rosacea? Do you use any sort of formal diagnostic tool during the process?

Dr. Del Rosso: There aren't any consensus definitions of mild, moderate, and severe rosacea in the clinical setting, so that delineation is often up to the investigator's overall visual "gestalt." The severity ratings are based on what are used in clinical trials for study purposes. You go in the room, you look at the patient, and you decide whether the patient's presentation is consistent with what you rate as mild, moderate, or severe disease based on global assessment definitions in the study protocol. In our minds in the clinic, we all probably have different thresholds, but I doubt there is much variation.

I was involved in a few projects with several colleagues where we were shown pictures from studies and asked individually whether we judged the patient to have mild, moderate, or severe disease. The results were generally close across the board, but I don't ever remember a case where one

person said an individual had mild disease and another insisted they had severe disease. This grading system discussion is only important for clinical research purposes.

Dr. Stein-Gold: At the end of the day, it really isn't terribly important if you judge a patient to have mild, moderate, or severe rosacea. A patient is a dynamic being. Maybe we would have judged them to have "mild" disease today, but yesterday they would have had "moderate" disease. And last week, when they were in a flare, they would have had "severe" disease. Because rosacea is such a cyclical disease, it needs to be treated based on a patient's symptoms over a course of time.

So while it's important in clinical trials to ensure that patients meet a specific standard of disease severity, in real life, our goal is to get patients clear regardless of the status of their disease on a specific day.

SETTING TREATMENT GOALS IN PATIENTS WITH PAPULOPUSTULAR ROSACEA

Dermatology Times: What are the primary considerations when recommending treatment options for a patient with papulopustular rosacea? How often is cost factored into the equation?

Dr. Webster: Cost is always a factor. Insurance companies are trying to take the management of

rosacea away from medical dermatology by calling it a “cosmetic” condition. Some insurance companies will make a patient fail 5 or 6 options before allowing them a trial of ivermectin, even with the clinical data we have showing its efficacy and safety.¹⁰⁻¹²

Cost alone, of course, isn’t the only determining factor. Whether a drug works to help with the patient’s primary presenting symptoms is a big deal. How bad the disease is to the patient is important. So is the question of whether the patient will use the medicine. Some people won’t put on a cream, while others won’t take a pill. The length of time they need to be on the medication is also an issue that is tied into cost.

So as dermatologists, we need to think about all of those things before deciding on a plan—in conjunction with the patient—that is going to have the best chance of being effective.

Dr. Baldwin: One thing I will often ask patients about is whether there is any deadline or important life event coming up for which they want to be better. Sometimes, the only reason a patient will come to see me is because, for example, their sister is getting married in a month, in which case I’ll often use a more aggressive combination topical/oral approach.

Dermatology Times: How do you approach a discussion with a patient with papulopustular rosacea who perhaps has overly

ambitious expectations of therapy?

Dr. Stein-Gold: This is one of our biggest challenges. Rosacea is a chronic disease. It isn’t something that a patient “got” last week like poison ivy. Many of our new patients will have seen on TV or online something that promises “RESULTS OVERNIGHT!” So, that is their expectation no matter how serious their symptoms. It’s our job to explain upfront the realities of treatment rather than wait to talk to the patients a few weeks or months later when their expectations haven’t been met.

What I usually focus on is a discussion of results we’ve seen from rosacea clinical trials. For instance, for topical medications, it might be 12 weeks before we see clearance of the skin. I will tell patients that we can expect to see

some of their bumps flattening in the first month, but we won’t see the skin clearing for a while.

The other thing I try to emphasize during the initial conversation is the importance of good skin care (**Table 1**). Many patients will often tell me that they have been using toners or other alcohol-based products that are not good for patients with rosacea. It’s important to get patients to stop using these irritating topical agents and focus on the importance of simple things like a gentle cleanser, moisturizer, and sunscreen.

Dr. Baldwin: Teaching patients how to utilize cosmetics to help conceal their erythema and perhaps even their papules while we wait for the medications to take effect is something I am

TABLE 1 SKIN CARE GUIDANCE FOR ROSACEA PATIENTS

| | |
|---|--|
|  | Cleanse your face—gently—at least once a day. |
|  | Apply moisturizer daily. |
|  | Protect your skin from the sun year round with sunscreen of SPF 30 or higher that offers broad-spectrum protection and does not irritate facial skin. |
|  | Choose rosacea-friendly skin care products. This includes avoiding products that contain alcohol, fragrances, and other ingredients. |
|  | Test new skin care products and makeup by applying a small amount near (but not on) your rosacea-prone skin. If it irritates your skin (burning, stinging, etc.) and continues to do so after 72 hours, do not use it. |
|  | Avoid rubbing or scrubbing your face. |

particularly passionate about. There is actually a funny sounding word for that: farding. It means, “To paint the face with cosmetics.”¹³

In my opinion, it’s very important for dermatologists to teach patients how to fard well and safely. Finding the right combination of moisturizers and sunscreens can be difficult in some rosacea patients who complain that, “Everything bothers my skin,” so it’s often a trial-and-error approach.

Dr. Bhatia: I like talking to new rosacea patients in terms of a “sprint” and a “marathon.” We know based on clinical trials that many of our agents will take 4 weeks to start working. That’s the sprint. The 16-week mark is our other key milestone. That’s the marathon.

Typically, I won’t ask to see a patient back in my office until we hit that 4-week mark, and with a drug like ivermectin, that may take 8 weeks to start showing demonstrable results.^{10–12} I’ll wait even longer.

I like talking to patients about a marathon because a marathon is about pacing, and with the treatment of rosacea—assuming that a patient remains adherent to treatment—you see a steady accumulation of benefits over time. Patients are investing a lot of time, energy, and money into these prescriptions, so it’s key to give them realistic expectations of when they can expect to see symptom improvement and how the improvement will build over time.

Dermatology Times: What are your primary initial treatment options in a patient you determine to have mild papulopustular rosacea?

Dr. Stein-Gold: I’ll often start with a topical agent. Topical ivermectin tends to be my treatment of choice if there aren’t any insurance issues. Otherwise, I’ll opt for topical 1% metronidazole or azelaic acid.

Dr. Webster: Simply to head off potential insurance challenges, I often try topical metronidazole before ivermectin. If a patient’s insurance company won’t cover either of those, I will typically resort to doxycycline 40 mg.

Dermatology Times: What about the approach in a patient you determine to have moderate papulopustular rosacea?

Dr. Del Rosso: I like to use a subantibiotic (subantimicrobial) dose of doxycycline if patients are willing to try an oral agent. The subantibiotic nature of the drug is key, and we’ll talk a little bit more about that later. Doxycycline can also be a good choice in patients who have adherence issues with topical agents.

There are some patients with moderate papulopustular rosacea who I will start on a combination of a topical agent and sub-antibiotic doxycycline. If I have a rosacea patient with both papules and pustules and background persistent erythema, I will try to

get them on a topical alpha agonist as soon as possible.

Dermatology Times: What about the approach in a patient you determine to have severe papulopustular rosacea?

Dr. Baldwin: In a patient with severe papulopustular rosacea, I like to start them on a combination of a topical agent such as ivermectin cream and either the 20 mg twice-daily or 40 mg daily controlled-release subantibiotic dose of doxycycline. Once the patient’s disease is under better control, I try to back off the combination and use either the topical or the oral alone, whichever the patient prefers.

Patients with rosacea of any severity who come to us are generally looking for immediate results, so it’s crucial to select a regimen that gives them the best chance of a rapid response.

Dr. Stein-Gold: For patients with really severe papulopustular rosacea, oral isotretinoin is always in the back of my mind, but it’s very rare that I need to try that. Today, we’re generally able to get even the most severe rosacea patients under control with topical/oral combination therapy.

Dermatology Times: Which topical/oral combinations are believed to be the most effective in treating papulopustular rosacea?

Dr. Stein-Gold: The data are

currently limited, although several ongoing trials are exploring the question. There are some data showing that a combination of topical ivermectin and topical brimonidine, started simultaneously, gets patients' symptoms under control more completely and rapidly than an initial start of ivermectin followed by brimonidine 1 month later.¹⁴ There have also been studies showing that a combination of either topical azelaic acid or metronidazole along with doxycycline—both a subantibiotic and higher dose—gets patients under control faster than the use of a topical agent alone.^{15,16}

There is an ongoing trial using a combination of topical ivermectin and low-dose doxycycline that may have future relevance for dermatologists.¹⁷

USE OF DOXYCYCLINE IN THE TREATMENT OF ROSACEA

Dermatology Times: Why is doxycycline believed to work in treating the inflammatory lesions of rosacea?

Dr. Webster: Doxycycline works because it's an anti-inflammatory agent, probably active through the inhibition protease activation of cathelicidin. It's also a neutrophil and is antigranulomatous, so it has a lot of anti-inflammatory effects that are active below the antimicrobial level.¹⁸

Dr. Del Rosso: Although there are

other tetracyclines such as minocycline that share some of the same anti-inflammatory properties of doxycycline, doxycycline is the only tetracycline for which researchers have been able to identify a dose-related threshold that is subantibiotic. That can be extremely important for our patients.

Dermatology Times: How does bacterial resistance to doxycycline develop?

Dr. Del Rosso: Any time a patient is exposed to an antibiotic, whether it be a topical or an oral agent, an antibiotic-resistant strain is going to emerge. It's just a fact of life. But in a rosacea patient, doxycycline is effective not because of its antibiotic effect, so why would we want to expose a patient to an antibiotic-resistant dose if we don't need to?

Dermatology Times: What is the threshold of antibiotic resistance for doxycycline?

Dr. Del Rosso: Several studies have shown that use of doxycycline either 20 mg twice a day or the 40 mg modified-release capsule once a day, administered over a prolonged period, is considered to be a subantibiotic dose. While there may be some limited emergence of bacterial-resistant organisms at these low doses, this has been minimal, and does not appear to persist over time, including controlled comparisons to placebo use.^{19,20}

If you choose to give higher doses of doxycycline to get more of an anti-inflammatory effect, you should be aware that your patients will develop antibiotic-resistant bacterial organisms, which can have negative longer-term impact.

Dr. Baldwin: While I agree with everything that Dr. Del Rosso said, if I have a patient with a particularly challenging history of rosacea who has tried and failed multiple options—and who was actually adherent to their previous regimens—I will often try a full 100-mg daily dose of doxycycline for a brief period. I've also had rosacea patients who do not respond to doxycycline but do respond to minocycline, although again, that's not something I will use for more than a couple of months before switching to a topical agent or a subantimicrobial dose of doxycycline for disease maintenance.

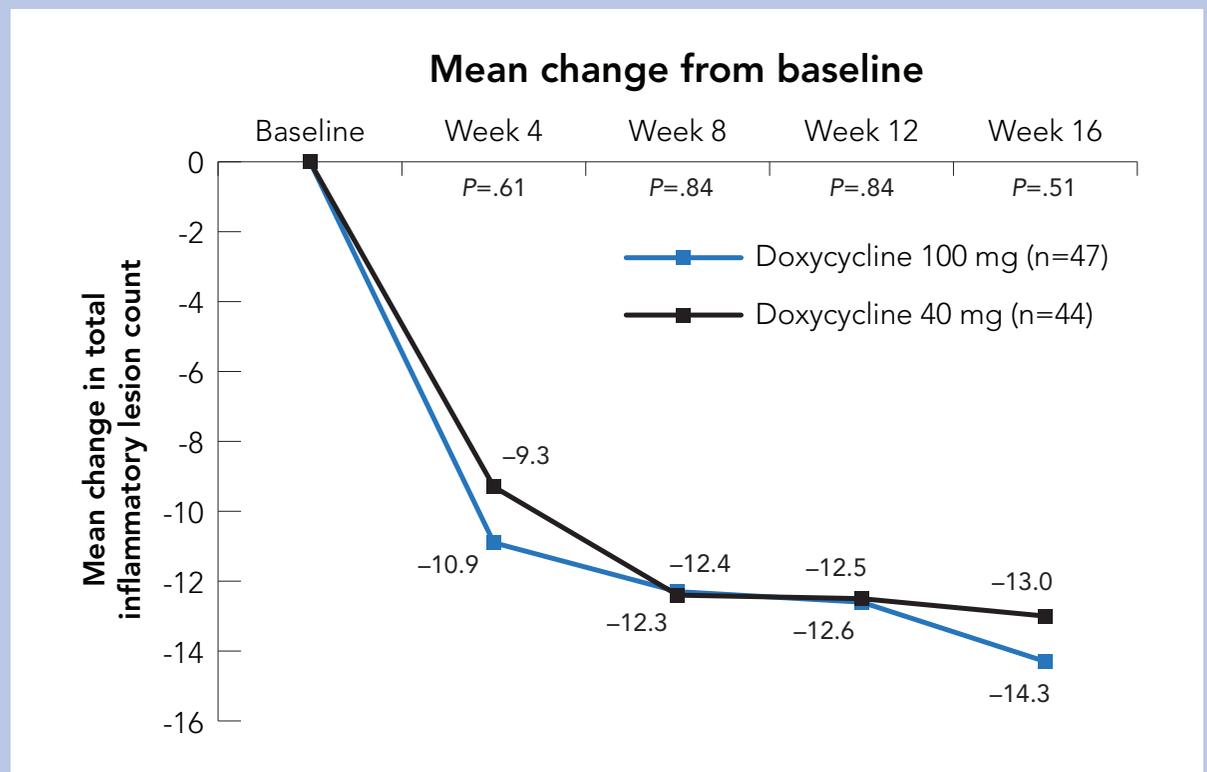
Dermatology Times: How do you determine what a "brief" period is?

Dr. Baldwin: That is great question. The answer is "as short as possible." You will often hear that we should not be using a full dose of an antibiotic for more than 3 months, but that's an arbitrary recommendation that is not based on any hard evidence. Antibiotic resistance begins after the very first pill.

Dr. Del Rosso: The other important factor to consider is not every patient will absorb a drug,

FIGURE 1 DOXYCYCLINE 40 MG VS. 100 MG

In a randomized, double-blind clinical trial, doxycycline 40 mg was shown to be equivalent to doxycycline 100 mg in regard to reducing inflammatory lesion count at all time points.



including an antibiotic, in the same fashion, and you will have some patients who are "low absorbers." Certain ingested substances that contain a high amount of metal ions, such as in foods or vitamin/mineral supplements/antacids, reduce the absorption of antibiotics such as minocycline and doxycycline to some degree.¹⁹ For those patients, a subantibiotic dose may not get them adequate improvement because they are absorbing only a

small amount of an already lower dose. Obviously, there is no easy way to tell upfront if you have a patient who is going to be a low absorber, but it is something to consider in a patient who does not respond to lower doses of doxycycline, or any other tetracycline given at a low dose.

I will usually give a patient a month on topical therapy and a subantibiotic dose of doxycycline before considering a higher dose of doxycycline. While I don't want

to give a patient a higher level of antibiotic, I don't sit there with a calendar and determine that I absolutely have to get them off antibiotic-dose doxycycline by a specific date in those selected cases when it is necessary. The antibiotic police aren't going to be lining up outside my door. I have to see improvement before I will ease a patient off the antibiotic dose. Getting a patient better is my top priority.

Dermatology Times: Is a higher dose of doxycycline (ie, 100 mg) more effective in treating papulopustular rosacea than a lower dose (ie, 40 mg)? What does the clinical evidence show?

Dr. Baldwin: In the average patient, the modified-release 40-mg dose of doxycycline has been shown to be noninferior to daily 100-mg doxycycline in regard to rapidity and duration of response (**Figure 1**).¹⁹ It certainly appears that the 40-mg dose is sufficient to give a patient the full anti-inflammatory effect.

Dr. Del Rosso: It's important to remember that in the primary clinical trial, patients were treated with daily metronidazole 1% in addition to doxycycline, either daily 40 mg modified release or daily 100 mg.¹⁹ The sponsor of the trial did not think it was wise to try to supplant topical treatment with oral therapy, but rather to enhance it. It was believed that dermatologists were not going to be interested in replacing topical therapy with an oral medication.

In truth, subantimicrobial dose doxycycline should not even be classified as an antibiotic. For a drug to truly be an antibiotic, it needs to reach the concentration to have an antibiotic effect. The other effects that doxycycline has in patients with rosacea—primarily its anti-inflammatory effects—are more consistent with biologic therapies than antibiotics.

Overall, I agree with Dr. Baldwin. Most patients respond well to

doxycycline 40 mg modified release capsules once daily when used as monotherapy or in combination with a topical agent.

Dermatology Times: Are there any key safety considerations for a patient who is prescribed doxycycline?

Dr. Webster: This may sound a bit obvious, but you do need to emphasize that doxycycline must be taken with a glass of water. Twice I have had patients who suffered esophageal perforations from taking doxycycline without liquids.

Dr. Stein-Gold: I have seen that happen as well. It's quite rare, of course, but it is something that is

really important to remind patients about.

Dermatology Times: Thank you to everyone for taking the time to discuss this timely and important topic. There are a series of key takeaways included near the back of this supplement that reinforce some of the highlights of this monograph (**Table 2**). We hope our audience finds this useful from a clinical perspective.

How do you treat rosacea patients?

Take our survey:

www.dermatologytimes.com/rosaceasurvey

TABLE 2 CLINICAL PEARLS

Make sure to treat the skin barrier before initiating drug treatment. Patients need to avoid the use of alcohol-based products, as well as harmful soaps or toners, and focus on appropriate use of a gentle cleanser, moisturizer, and sunscreen.

Look at all the visible manifestations of new and follow-up rosacea patients, and target your therapeutic approach to impact all of a patient's symptoms.

Remind patients that rosacea is a chronic disease whose visible signs and symptoms will not resolve overnight. Patience is often necessary before significant gains are noted.

Rosacea medications are typically appropriate for specific rosacea clinical manifestations and do not address all of the signs of rosacea. Patients with multiple rosacea manifestations will typically require a combination of at least two agents to reach a clear status.

FDA-approved agents for the treatment of rosacea are generally appropriate for long-term treatment and, overall, do not need to be discontinued at a specified time point due to safety concerns. In fact, the chronic nature of rosacea suggests that long-term treatment is often the best approach in many patients.

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