Optimizing the Use of Topical Brimonidine in Rosacea Management: Panel Recommendations

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ABSTRACT

Rosacea is a chronic inflammatory disease with a complex pathophysiology that manifests with central facial redness with or without papulopustular lesions. Often, patients with rosacea present with a constellation of signs and symptoms; for best results, the treatment plan should take into account all symptoms manifesting in the individual patient. The first available pharmacologic treatment to address the redness associated with rosacea is topical brimonidine. In the United States, brimonidine topical gel 0.33% is indicated for persistent facial erythema of rosacea; approval was based on clinically significant efficacy and good safety data from large-scale clinical trials. Use of brimonidine 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 (in our experience, approximately 10 to 20%) treated with brimonidine experience a worsening of erythema that has been called "rebound." Our routine use of this agent for >1 year has yielded strategies to set patient expectations, optimize treatment initiation, and minimize potential problems; this article details those strategies. Because we believe that the term "rebound" has been used to describe several physiologically distinct events, we have also proposed more specific terminology for such events.

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INTRODUCTION

The clinical features of rosacea, including facial redness, papules/pustules, flushing and, oftentimes, skin sensitivity, have long been known.[1-3] New information from molecular-level studies has shown that rosacea is an extremely complex disease with multiple aberrancies occurring in a variety of cutaneous neural, immune, and vascular pathways.[4-8] An understanding of these pathways has given dermatologists a better knowledge of the most appropriate treatment options for this disease.[2, 4, 5] It is not the purpose of this article to review the clinical presentations of rosacea, as these have been covered elsewhere.[9, 10] It should be noted that while rosacea can be categorized into subtypes based on clinical presentation (erythematotelangiectatic rosacea, papulopustular rosacea, phymatous rosacea, and/or ocular rosacea), most experts today view rosacea as a chronic inflammatory disease with a spectrum of clinical features that can wax and wane over time.[2, 11, 12] In 2013, the American Acne and Rosacea Society recommended that "rosacea management is best approached via assessment of the spectrum of clinical manifestations present in each individual patient."[12] New additions to the rosacea treatment armamentarium – like topical brimonidine gel 0.33%, the first treatment approved for topical treatment of persistent (nontransient) facial erythema (US indication) of rosacea – have prompted clinicians to re-assess the overall approach to this complex disease.

Facial redness is an extremely common finding in patients with rosacea, affecting up to 87% of rosacea sufferers; it can be present in all subtypes of rosacea.[13] The erythema associated with rosacea poses a challenge for patients and clinicians alike.[5] Both vascular and inflammatory events are involved in the clinical manifestations of redness.[4, 6] The complete pathophysi-

ology of this disease is far from clear at this time.[2] However, it is known that facial redness due to vascular changes can be transient or persistent.[5] Papulopustular lesions often have associated redness (lesional or perilesional) which is different from generalized vascular erythema.[5, 10, 14] Finally, specific events of flushing may occur via a different mechanism than generalized erythema of rosacea and should clearly be differentiated from physiologic blushing, which occurs involuntarily in response to emotional and other stressors (eg, embarrassment).

Brimonidine is an alpha-2 adrenergic agonist that, when applied topically, causes peripheral vasoconstriction via a direct effect on smooth muscle-receptors.[15-17] It is thought that the vasoconstrictive action of topical brimonidine gel counteracts abnormal dilation of facial blood vessels in patients with rosacea. The safety and efficacy of brimonidine gel in rosacea were evaluated in two large-scale, controlled phase III studies and a long-term safety study.[16, 17] Together, these studies enrolled 992 subjects, 726 of whom were treated with brimonidine gel.[16, 17] The phase III studies showed that brimonidine gel was significantly more efficacious than its vehicle throughout the study duration; in addition, it had a good safety profile.[17] The long-term study also showed that brimonidine gel works well in the management of facial erythema of rosacea and demonstrated that brimonidine can be used safely at least for a period of 12 months.[16] As the first drug approved for the treatment of facial erythema of rosacea throughout the world, brimonidine gel can have an essential role in the overall management of rosacea. Since its introduction, there have been reports in the literature and in informal communications on a "rebound" or worsening of redness that can occur during brimonidine gel therapy.[18, 19] This article, written by a group of dermatologists with more than 1 year of hands-on experience with brimonidine (including as clinical trial investigators), is designed to help guide clinicians in the use of brimonidine gel as part of a rosacea treatment plan.

Because we believe that brimonidine gel is an important therapeutic option addressing a key unmet need in rosacea, we have listed here detailed steps that may be used to optimize efficacy and minimize the potential for adverse events including the phenomena often called "rebound" worsening of erythema. We also propose more specific terms to clarify the onset and type of erythema that has occurred.

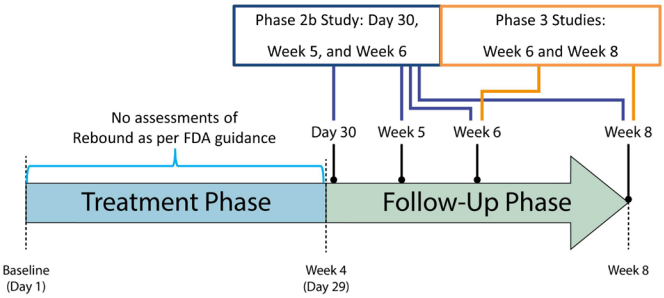
A Closer Look at Brimonidine-Associated "Rebound" Phenomena

"Rebound" phenomena or treatment-related erythematous events have been reported in brimonidine clinical trials, literature, post-launch spontaneous safety reporting (pharmacovigilance), and in informal communications such as patient websites and physician meetings.[13, 17-19] This section discusses the events that have been grouped together and categorized as "rebound" and provides recommendations for assessing redness associated with brimonidine therapy based on available data and our clinical experience.

"Rebound" in the Brimonidine Clinical Development Program

Traditionally, "rebound" is defined as the emergence or re-emergence of symptoms that were absent or controlled during treatment, but appear after discontinuation of treatment or when the dosage is reduced. In the case of re-emergence, the severity of the symptoms is often worse than pretreatment levels.[20] In the early stages of brimonidine clinical development for rosacea, the US Food and Drug Administration (FDA) provided guidance to the drug's manufacturer that "rebound" should be defined as worsening of subject's rosacea after cessation of brimonidine gel therapy. As shown in Figure 1, the term "rebound" was not used for any worsening of redness events during the active phase of the brimonidine gel studies (any redness event during the active phase was recorded as an adverse event); all assessments of "rebound" in the clinical studies occurred after discontinuation of therapy.[13]

FIGURE 1. Timepoints for assessment of rebound during clinical studies.[13]



Data on file, Galderma Laboratories.

In their presentation of the phase III clinical study results, Fowler et al reported that there was "no rebound or worsening of erythema" during the "4-week follow-up phase" after brimonidine therapy had been discontinued.[17] In accordance with the clinical trial protocol, Fowler et al were utilizing the FDA definition of rebound as an event occurring after cessation of therapy. During the treatment phase of the study, the researchers reported worsening of erythema and/or flushing as the most frequent treatment-related adverse events; these were not recorded as "rebound."[17]

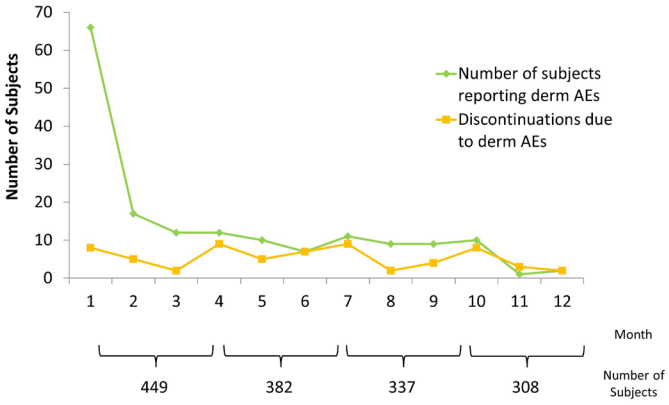
After receiving spontaneous reports of worsening erythema in clinical practice after the drug became available in the US, data from the clinical studies were re-analyzed to determine if signals of rebound/worsening could be detected during the active treatment period.[13] A thorough discussion of this analysis is being prepared as a separate publication by the study sponsor. The reported adverse events that could have been suggestive of a worsening phenomenon were: erythema/worsening of

TABLE 1.

Dermatological Treatment-Related Adverse Event Incidence, Severity, and Discontinuations in Phase III Clinical Studies of Brimonidine Gel.[13]

Number of Events (%)					
	Total	Mild	Moderate	Severe	Discontinuation
Brimonidine (n=277)					
Erythema	10 (3.6%)	4 (1.4%)	6 (2.2%)	–	1 (0.4%)
Pruritus	6 (2.2%)	5 (1.8%)	1 (0.4%)	–	–
Flushing	6 (2.2%)	5 (1.8%)	1 (0.4%)	–	–
Skin discomfort/burning/pain	5 (1.8%)	4 (1.4%)	1 (0.4%)	–	–
Rosacea	4 (1.4%)	3 (1.1%)	1 (0.4%)	–	–
Irritation/dermatitis	4 (1.4%)	3 (1.1%)	–	1 (0.4%)	1 (0.4%)
Vehicle (n=276)					
Irritation/dermatitis	6 (2.2%)	6 (2.2%)	–	–	–
Rosacea	3 (1.1%)	3 (1.1%)	–	–	–
Pruritus	3 (1.1%)	3 (1.1%)	–	–	–
Skin discomfort/burning/pain	2 (0.7%)	2 (0.7%)	–	–	–
Erythema	2 (0.7%)	2 (0.7%)	–	–	–
Rash	1 (0.4%)	1 (0.4%)	–	–	–

FIGURE 2. Time to onset of dermatological adverse events in 12-month brimonidine safety study.[13]



Data on file, Galderma Laboratories.

erythema, flushing, rosacea, skin warm, skin discomfort and irritation/dermatitis. Table 1 presents the frequency of those adverse events in the phase III trials.[13]

The discontinuation rate for dermatological adverse events occurring in >1% of total subjects was 0.8%. The time to onset of dermatological adverse events and discontinuations due to these events during the 12-month long-term study of brimonidine gel are shown in Figure 2.[13]

As detailed in Figure 2 and Table 2, the majority of these adverse events occurred in the first two weeks of the long-term study, and were mild to moderate in severity.[13, 16] The data show no clear relationship between baseline numbers of papules/pustules and frequency of adverse events. Of interest, the majority of dermatologic events were not observed by investigators or documented with photographs, but rather were reported in patient diaries.[13] It is important to note that discontinuation due to dermatologic adverse events occurred at a low and relatively steady rate throughout the study.[16]

Reports of "Rebound" in the Literature

In 2014, Ilkovitch et al[18] published one case and Routt et al[19] reported three cases of "rebound" in patients treated with brimonidine gel. The events reported in these instances happened within 24 hours after the first application of brimonidine gel and as such do not fit the traditional definition of "rebound" as occurring after a treatment course has finished.[18, 19] Each could, however, potentially be considered an exaggerated recurrence of erythema. In the single case reported by Ilkovitch et al, brimonidine gel effectively relieved redness but erythema recurred 10-12 hours after application (an expected return); unexpectedly, the erythema was worse than baseline.[18] The worsened erythema persisted for 12-14 hours then resolved spontaneously.[18] Continued use of brimonidine gel resulted in similar outcomes.[18] In our opinion, this should be called *exaggerated recurrence of erythema*, indicating an erythema that occurs after the drug effect subsides and has severity greater than baseline.

The cases reported by Routt et al also involved worsening erythema after the first application of brimonidine gel.[19] In these cases, erythema improved for 1-6 hours but then worsening redness occurred. In two cases, the patients continued use of brimonidine for several days until additional symptoms were noticed (burning

TABLE 2.

Time to Onset and Frequency of Adverse Events in >1% of Subjects Receiving Brimonidine Gel in 12-Month Safety Study[13]

Dermatological Related Adverse Events Over 52 weeks										
Adverse Event	Events in First 29 Days, n (n=449)	Events, n				Events Over 52 Weeks, n	Events, n			
		W1	W2	W3	W4		Q1 (n=449)	Q2 (n=382)	Q3 (n=337)	Q4 (n=308)
Flushing	25	15	4	3	3	45	34	5	5	1
Erythema	21	5	6	8	2	46	37	4	2	3
Skin Discomfort	11	7	1	2	1	22	16	4	2	0
Rosacea	8	5	1	0	2	16	11	2	3	0
Skin Warm	6	5	0	1	0	9	7	1	1	0
Pruritus	5	3	1	1	0	11	6	3	2	0
Dermatitis	4	1	2	0	1	46	7	14	15	10
Dryness	4	4	0	0	0	6	4	0	1	1
Rash	1	1	0	0	0	7	2	2	3	0
Total events	**85**	**46**	**15**	**15**	**9**	**208**	**124**	**35**	**34**	**15**

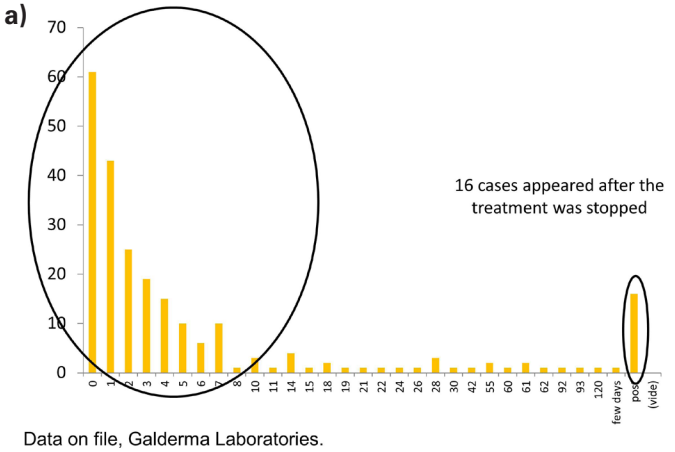
sensations).[19] The third patient experienced additional symptoms (burning, pruritus) with the initial application.[19] In all cases, the adverse events resolved spontaneously within one day.[19] Routt et al recommended several useful strategies for clinicians prescribing brimonidine gel, including: 1) counseling patients about the potential for worsening erythema (perhaps showing a photo of worsening redness) and 2) utilizing a test area before applying the medication to the full face.[19] In our opinion, this relatively immediate reaction (with or without additional symptoms such as burning) could be considered a *paradoxical erythema.*

Pharmacovigilance Data

Following the introduction of a new drug, suspicions of adverse reactions may be reported to the drug's manufacturer by prescribers or patients. The cases reported to Galderma, manufacturer of brimonidine gel, have been analyzed to evaluate trends in post-marketing safety signals.[13] The analysis of case reports qualified as "condition aggravated" or "rebound effect" by the reporter received from launch to end of April 2014 showed that the most frequently associated symptoms were erythema in nearly all cases, flushing, feeling hot/skin burning sensation/skin warmth, and more rarely skin pain. Dermatitis, pruritus, swelling face, and pallor were found in fewer than 10% of reports each. Because these were spontaneous reports, there is limited information about patient characteristics and risk factors, including clinical type of rosacea, exposure to rosacea triggers or exacerbating factors, concomitant treatments, or medical history.[13]

As shown in Figure 3, "conditions aggravated/rebound effects" were most likely to occur in the first 15 days after initiation of therapy, primarily in the first week (when data were available); in addition, two distinct peaks in time to onset of erythematous event after application of brimonidine gel have been reported (3-6 hours and 10-12 hours).[13] This allowed identification of two types of reactions based on the time to onset post application: appearing within 3-6 hour and observed after 10-12 hours.[13]

FIGURE 3. Trends in time to onset of events reported as condition aggravated/rebound effect from pharmacovigilance data. **A)** Days after initiation of therapy and **B)** hours after application.[13]



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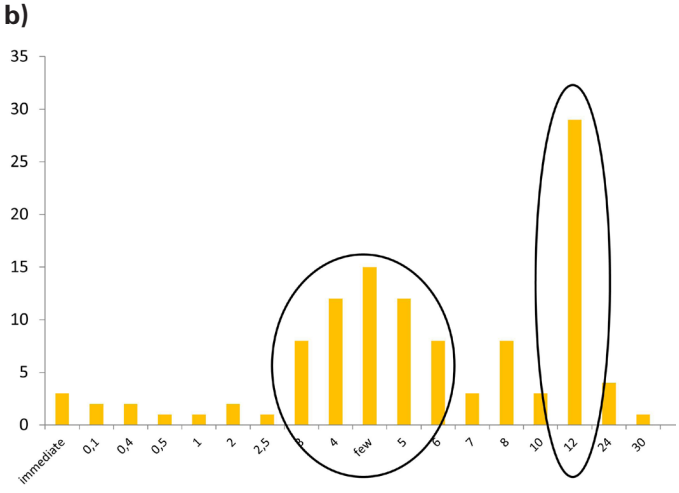


Data on file, Galderma Laboratories.

As reported in the cases published in the literature, typically there is a rapid recovery.[13, 18, 19] Rarely, an event may last weeks. In a majority of cases, the event improved or resolved after stopping brimonidine therapy.[13]

Less Formal Reports of "Rebound"

Dermatologic meetings and other informal communications have yielded comments about "rebound" that encompass changes in redness that happen at a variety of time points after initiation of brimonidine therapy. Given further analysis of existing data, it seems that these comments likely refer to different pathophysiologic phenomena. As discussed above, some patients experience a worsening of redness, either occurring shortly after application (within first 6 hours) that we propose to qualify as *paradoxical erythema* (see below proposed new terminology) or an *exaggerated recurrence of erythema* after the effects of the first application have subsided (approximately 10-12 hours after application). Our clinical experience has been that the *paradoxical erythema* phenomenon is most bothersome for patients, particularly since it often strikes during the time period when the patient most wanted to be free of their redness; in contrast, *late exaggerated recurrence of erythema* is most likely to occur while the patient is at home or even sleeping.

We have heard colleagues use the term "rebound" in reference to patients who were not satisfied with the drug effect for individual reasons and voiced this complaint to their physician. For instance, some patients may not appreciate a beneficial effect with brimonidine gel on overall facial erythema when redness due to perilesional erythema and/or telangiectasia is unmasked and lesions become more visible. Others may feel the product results in "overwhitening." In addition, irritation may occur at any time during the course of drug exposure.

Proposed new terminology for changes in redness during and after brimonidine therapy based on emerging evidence

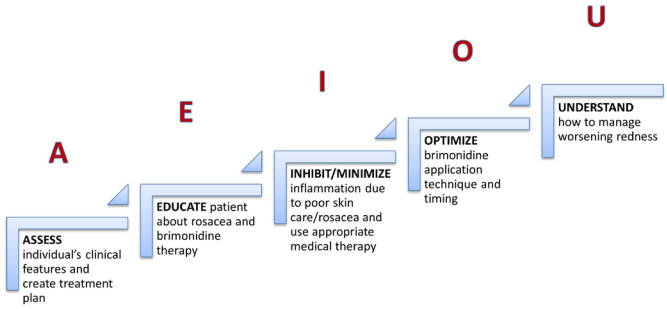
1. **Paradoxical erythema** – redness appearing within 3-6 hours after application of brimonidine (redness can be worse than baseline).
2. **Return to baseline erythema** as therapy wears off (10-12 hours after application). This is included for completeness but will not be discussed further.
3. **Exaggerated recurrence of erythema** - redness greater than baseline that occurs as therapy wears off (10-12 hours after application).
4. **Allergic contact dermatitis** – redness (usually accompanied by other signs such as pruritus) that typically occurs 3-4 months after initiation of therapy.

In addition, irritation may occur at any time during the course of drug exposure.

Recommendations for use of Brimonidine in Persistent Redness of Rosacea

As shown in Figure 4, there are several overall steps that should be considered with the initiation of brimonidine therapy for redness of rosacea and these steps can readily be remembered.

FIGURE 4. General steps when using brimonidine as part of rosacea management plan.



Assess rosacea. First, assess ("A") the clinical features of rosacea to confirm the diagnosis and rule out alternatives such as acne, seborrheic dermatitis, perioral dermatitis, lupus erythematosus, photoaging, facial keratosis pilaris, or chronic actinic dermatitis. Then, create the overall treatment plan, targeting the different clinical symptoms of rosacea that are present in the individual patient.[21]

"New additions to the rosacea treatment armamentarium – like topical brimonidine gel 0.33%, the first treatment approved for topical treatment of persistent (nontransient) facial erythema (US indication) of rosacea – have prompted clinicians to re-assess the overall approach to this complex disease."

Provide patient education. Educate ("E") the patient about rosacea, taking care to explain triggers (for example: UV light exposure, heat, spicy foods, red wine or other factors the patient associates with symptoms),[21] and discuss the potential benefits and limitations of brimonidine therapy. Use of brimonidine will not completely negate the erythema-inducing effects of triggers, and patients should be aware that brimonidine therapy does not afford carte blanche to ignore potential triggers. Further, brimonidine will not eliminate papules, pustules, or telangiectasias and is not a curative therapy.[16, 17] In our experience, setting appropriate expectations for patients can significantly minimize the likelihood of dissatisfaction with therapy and the clinician.

Setting Patient Expectations

In our experience, setting appropriate patient expectations is extremely useful with brimonidine therapy. Recommended educational messages for patients new to brimonidine are listed below. The clinician may prefer to prepare the barrier of the skin before starting brimonidine if the skin is irritated or inflamed.

- The normal effect of brimonidine is localized cutaneous vasoconstriction reducing erythema that lasts 8-12 hours
- Brimonidine is a drug and like any drug can induce adverse events
- Brimonidine has been developed for once daily use
- Brimonidine may not negate all erythema-inducing effects of rosacea triggers and patients still need to be aware of and avoid exposure to triggers
    - Good skin care and use of broad spectrum moisturizing sunscreen is important for all rosacea patients
    - There is a risk for worsening of redness (~10-20% of patients)
    - When it occurs, worsening redness usually develops within the first 2 weeks
    - It may be seen soon after initiation of therapy (3-6 hours) or after the effects of treatment have subsided (10-12 hours)
    - Generally, worsening redness resolves spontaneously after treatment discontinuation and within 12-24 hours
    - The physician should be consulted in the case of prolonged redness or additional symptoms such as prolonged skin warmth, burning/stinging, or itching

Inhibit/minimize inflammation. Take appropriate steps to inhibit/decrease the inflammation ("I") that is often present due to poor skin care and the disease itself.[1, 21] These steps can include evaluating/changing skin care practices and using medical therapy.[1] We find that patients commonly have poor skin care habits which, when combined with rosacea, result in sensitive skin and often compromised barrier function. Because irritation and problems with topical therapies are more likely to occur in this setting,[1] evaluate the patient's skin barrier function and improve if needed. Improving barrier function can be achieved by 2-4 weeks of using gentle, well-formulated cleanser and moisturizer/barrier repair products prior to starting topical brimonidine therapy.[1] The American Acne and Rosacea Society recommends choosing products that repair/maintain barrier function, enhance skin hydration, and minimize irritation.[1] Rosacea management should also include regular photoprotection using both sun avoidance and a broad-spectrum sunscreen/sunblock with a sun protection factor of 30 or higher.[1] Patients should also be reminded that brimonidine has no sun protective effect and therefore appropriate daily sun protection is advised.

It is our experience that the *paradoxical erythema* phenomenon (redness occurring 3-6 hours after application) may be minimized by skin barrier repair and a "start low, go slow" approach to dosage (see below).

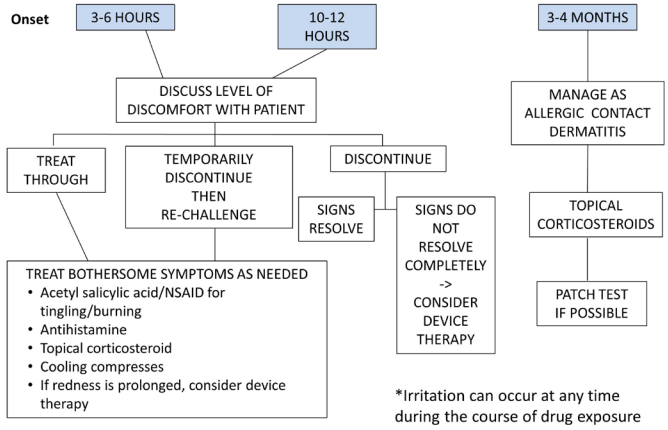
Minimize rosacea-associated inflammation using traditional rosacea therapies.[21] Treat inflammatory lesions when present.[21] They will be more visible after the use of brimonidine and patients may be distressed by this. Educate patients about perilesional erythema and telangiectasias, and inform them that these skin characteristics may become more visible once brimonidine gel reduces the overall facial erythema. It can also be useful to screen for frequent flushing, since it has been theorized that patients who flush have particularly labile skin that is prone to undesired redness with brimonidine.

Optimize application of brimonidine. Teach patients to properly apply the medication in a very thin layer, optimizing ("O") their application techniques and starting with a very small pea size amount (once daily). Start with this smaller amount of medication and increase the amount as the patient gains experience. It is important to ensure that patients are continuing their moisturizer/barrier repair product along with the topical brimonidine. Have a staff member show the patient how to apply brimonidine in a uniform distribution. We have also found that it is useful to instruct patients to try the first application of brimonidine on a day when they can stay home most of the day to observe effects; this could be on a weekend or vacation day. Judicious use of samples may be beneficial in this regard. Although it is common sense, patients should be made aware that they should not apply brimonidine at bedtime and may adjust the timing of their dose based on their daily routine and/or special events. Intermittent use of this drug has not been studied and it is difficult to predict the side effect profile when used in this manner.

"Traditionally, "rebound" is defined as the emergence or re-emergence of symptoms that were absent or controlled during treatment, but appear after discontinuation of treatment or when the dosage is reduced. In the case of re-emergence, the severity of the symptoms is often worse than pretreatment levels."

Understand worsening redness may occur. Last, understand ("U") that there is the potential for a worsening of erythema. Figure 5 presents an algorithm for managing worsening redness, which in our clinical experience may occur in approximately 10-20% of cases. First, determine the timing of worsening redness relative to application, then decide together with the patient whether to continue therapy or discontinue with or without re-challenge. Treat symptoms as needed. In the appropriate patient, we recommend using acetyl salicylic acid (80-500 mg/day) or another nonsteroidal anti-inflammatory drug (NSAID) such as ibuprofen or naproxen if burning/stinging sensations are present, an antihistamine if swelling or pruritus is occurring, and a topical corticosteroid if needed.[13] Topical calcineurin inhibitors may also be considered. Cooling compresses may also help patients who feel facial warmth. If redness is prolonged, device therapy might be a consideration. For the rare cases of redness that first appear late after initiation of therapy (>3-4 months), manage as a suspected allergic contact dermatitis and consider patch testing to rule out contact allergies. An augmented index of suspicion is warranted because allergic or irritant contact dermatitis could occur during therapy at the 3-4 month time point or earlier, especially if the patient has a history of sensitivity to the excipients in brimonidine gel, extremely sensitive skin, or previous exposure to brimonidine eye drops.

FIGURE 5. Algorithm for managing worsening redness associated with brimonidine gel therapy.

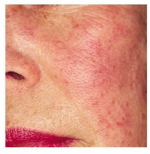


PATIENT HANDOUT

When Your Doctor Has Prescribed Brimonidine

In general:

- Remember, brimonidine is a treatment not a cure
  - Responses vary
  - Brimonidine does not treat pimples or red veins – your doctor may prescribe other medications for these problems



- You can quickly tell whether you like the effects of brimonidine
  - Try it for the first time on a day when you can stay home and watch the effects
  - Apply the medication in a very thin layer, optimizing ("O") application technique and starting with very small pea size amount. Start with this smaller amount of medication and increase the amount as you gain experience

- Be kind to your skin
  - Use a gentle skin cleanser and moisturizer
  - Use a broad spectrum sunscreen

If bothersome redness occurs

1) OBSERVE	2) SOOTHE	3) CONTACT DOCTOR
•Wait and watch: redness may subside on its own	•For burning or tingling – aspirin or other NSAID •For swelling – antihistamine •Cooling compresses or ice may also feel good	• Your doctor may prescribe other medications

CONCLUSION

Facial redness is a primary concern for many patients with rosacea, and brimonidine is an important new therapy that can have a vital role in helping clinicians manage this complex disease. As with any drug, side effects can occur. In our experience, the side effects that have been grouped together as "rebound" really include several different phenomena: paradoxical erythema, expected return of erythema after the drug effects subside, an exaggerated recurrence of erythema, patient dissatisfaction with appearance of lesional erythema and telangiectasia that were not affected by brimonidine, and, contact dermatitis that, in rare cases, may be allergic in nature. Including brimonidine in an overall rosacea management plan should not be viewed as challenging – taking several simple steps as outlined above can avoid many problems and help to minimize any that do occur.

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DISCLOSURES

Drs. Tanghetti, Jackson, Belasco, Hougier, and Johnson are advisors, investigators and speakers for Galderma Laboratories, L.P. Drs. Friedrichs, Hong and Hinek are advisors for Galderma. Dr. Palceski is an advisor and speaker for Galderma Laboratories, L.P. Dr. Kerdel is an advisor and investigator for Galderma Laboratories. Dr. Rueda Cadena is an employee of Galderma Laboratories, L.P.

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