

A Tailored Approach to the Treatment of a Patient with a Severe Dynamic Manifestation of Rosacea: A Case Report

Martin Schaller¹ · Lena Gonser¹

Published online: 13 September 2016
© The Author(s) 2016. This article is published with open access at Springerlink.com

Abstract Rosacea is a chronic inflammatory disease that can manifest as a spectrum of symptoms including erythema, inflammatory lesions, edema, and telangiectasia. Treatment decisions need to be adapted to reflect the nature and severity of the different symptoms present. In this report, we discuss the case of a female patient diagnosed with severe, inflamed papulopustular rosacea (PPR) presenting with a large number of inflammatory lesions and severe background erythema. This patient responded well to a treatment regimen consisting of a short course of antibiotics in combination with a corticosteroid, followed by monotherapy with isotretinoin to reduce the inflammation. Brimonidine gel, used as needed, was then added to isotretinoin to target the remaining background erythema. This case of severe PPR required a combinatorial treatment regimen to effectively target all symptoms present. The patient continued to apply topical metronidazole throughout the different treatment regimens prescribed over the course of almost 1 year. Use of topical metronidazole helped to repair and protect the skin barrier, which minimized the occurrence of dermatological adverse events when topical treatments were used. We conclude that in patients with severe disease and an important inflammatory component, a rapid response can be obtained with a multimodal, tailored approach that also includes treatment to repair and protect the skin barrier.

Key Points

A patient with severe papulopustular rosacea (PPR) and severe background erythema responded well to a treatment regimen consisting of a short course of antibiotics in combination with a corticosteroid, followed by monotherapy with isotretinoin.

In patients with very severe, inflamed disease, it is necessary to achieve a rapid response with a fast-acting combinatorial treatment regimen to reduce the inflammation.

Patients with severe PPR and an inflammatory component can respond rapidly when treated using a multimodal, tailored approach.

1 Background

Because rosacea presents as a spectrum of overlapping symptoms of variable severity, it is important to adapt treatment decisions to individual clinical presentations. Papulopustular rosacea (PPR) is a commonly encountered subtype of rosacea characterized by the presence of persistent central facial erythema (background erythema), accompanied by central facial inflammatory lesions (papules and/or pustules) [1].

Patients with PPR often present with lesional and perilesional erythema, which is found around and immediately contiguous to a papule or pustule and contributes to the overall appearance of facial redness [2]. Agents currently approved for the treatment of the inflammatory lesions of rosacea are known in clinical practice for their additional

✉ Martin Schaller
martin.schaller@med.uni-tuebingen.de

¹ Department of Dermatology, Eberhard Karls University Tübingen, Liebermeisterstrasse 25, 72076 Tübingen, Germany

effect of decreasing the overall severity of facial erythema, as a result of the reduction of the lesional and perilesional erythema. However, these agents are not indicated in the treatment of background erythema, which typically persists after clearance of the inflammatory lesions [2].

Alternative treatments for the symptoms present in patients with PPR include short courses of second-generation macrolides such as clarithromycin and azithromycin, which have demonstrated a fast onset of action and a good safety profile in the treatment of patients with PPR [3, 4]. These agents may therefore prove useful as an off-label treatment in patients with severe disease who do not respond to tetracycline therapy, or when isotretinoin is contraindicated [5]. In addition, although corticosteroids are not indicated for use in rosacea, their short-term use may be considered in patients with severe disease who present with signs of rosacea fulminans [6].

There is an increasing awareness of the need to repair and protect the skin barrier as part of the treatment strategy when prescribing treatments aimed at strongly targeting the inflammatory component. It is known that an impaired skin barrier leads to a heightened and potentially chronic inflammatory response. Repairing and protecting the skin barrier will decrease the risk of this process occurring, while also reducing the incidence of dermatological adverse events [7, 8].

Here, we report a case of severe PPR with an important inflammatory component. A strategy aimed at strongly targeting the inflammation upfront was successfully implemented before addressing the remaining background erythema component.

2 Case Description

In May 2014, a 30-year-old Caucasian woman presented to our department (Fig. 1a). For the past 4 years, the patient had suffered from severe PPR (principally on the forehead, cheeks, and chin) with signs of rosacea fulminans, as well as severe background erythema in the central facial and forehead regions. She had previously been treated with metronidazole 7.5 mg/g cream and permethrin 50 mg/g cream, which had not provided a reduction in the number of inflammatory lesions. She had also been prescribed doxycycline modified-release 40 mg for 18 months, which had also proved unsuccessful in reducing the inflammation.

At presentation, the patient reported feelings of hopelessness, indicating a profound impact of the disease on her quality of life. Following diagnosis of PPR with severe background erythema, different treatment options were evaluated. In such a severe case, a specific strategy tailored to the patient was essential, particularly given the lack of success with prior regimens, which seemed to indicate that

a more potent treatment regimen was needed in this patient to combat the inflammation upfront. Isotretinoin was initially considered; however, because the patient was not taking hormonal contraception at the time of her visit to our department, this therapy was contraindicated. The patient was offered a gynecology appointment to start hormonal contraception, so that isotretinoin could be an option in the future. The patient was initially prescribed an 8-week regimen of azithromycin 500 mg three times weekly (taken in the morning) in combination with prednisolone 30 mg once daily (reduced to 10 mg once daily after 1 week). The choice of this regimen was based on results from the literature showing that a rapid response can be obtained with a multimodal, tailored approach with a short course of macrolide antibacterials [4]. Furthermore, the use of corticosteroids over the short term is not strictly contraindicated in the treatment of rosacea and can be considered as an option to reduce inflammation in patients who present with signs of rosacea fulminans [6]. Metronidazole 7.5 mg/g cream twice daily was continued with this combination therapy.

After 4 weeks of treatment, a reduction in the inflammatory lesion count was observed (Fig. 1b). A slight decrease in the severity of facial redness was also seen, especially on the forehead, most likely resulting from a reduction in lesional and perilesional erythema. The patient continued to take azithromycin 500 mg three times weekly and the prednisolone dose was reduced to 5 mg once daily. In addition, the patient continued to apply metronidazole 7.5 mg/g cream twice daily.

During examination of the patient's face 1 month later, only a small number of inflammatory lesions were present (Fig. 1c). The severity of erythema remained similar to that observed during the previous visit, indicating a reduction in the severity of the inflammation. Therapy with azithromycin 500 mg three times weekly and prednisolone 5 mg once daily was stopped; treatment with isotretinoin 10 mg once daily (taken with the main meal) was initiated, and application of metronidazole 7.5 mg/g cream twice daily was continued.

When the patient returned to our department 4 months later, no inflammatory lesions were present; however, the erythema had worsened on the forehead and cheeks (Fig. 1d). The patient continued to apply metronidazole 7.5 mg/g cream twice daily, as well as isotretinoin 10 mg once daily for further improvement and as maintenance therapy to prevent relapse of inflammatory lesions. Treatment with brimonidine 3 mg/g gel, used as needed and applied in the morning, was initially started to the left side of her face in order to assess the impact of this agent on the background erythema (split-face assessment). Brimonidine, a highly selective α_2 -adrenergic receptor agonist [9], is approved for the symptomatic treatment of facial erythema



Fig. 1 Patient with rosacea presenting with overlapping symptoms of severe inflammatory lesions and severe background erythema, receiving sequential treatment with azithromycin 500 mg plus prednisolone, isotretinoin 10 mg, and topical brimonidine 3 mg/g gel; topical metronidazole 7.5 mg/g was administered throughout the entire period. **a** May 2014 (baseline): patient with severe papulopustular rosacea, with signs of rosacea fulminans, and severe background erythema at initial presentation. **b** June 2014 (4 weeks after baseline): 4 weeks after initiation of treatment with azithromycin 500 mg three times weekly plus once-daily prednisolone (30 mg for 1 week; 10 mg for 3 weeks), in combination with metronidazole 7.5 mg/g cream twice daily. **c** July 2014 (8 weeks after baseline): following a further 4 weeks of azithromycin 500 mg three times weekly, in combination

with once-daily prednisolone 5 mg treatment; the patient continued to apply metronidazole 7.5 mg/g cream twice daily. Isotretinoin 10 mg once daily was started. **d** October 2014 (25 weeks after baseline): following 4 months of treatment with isotretinoin 10 mg once daily. **e** December 2014 (32 weeks after baseline): following a further 2 months of treatment with isotretinoin 10 mg once daily in combination with brimonidine 3 mg/g gel applied to the left side of the face 3 h before presentation to our outpatient department. **f** March 2015 (43 weeks after baseline): following an additional 3 months. Treatment with isotretinoin 10 mg once daily was stopped after 9 months; treatment with metronidazole 7.5 mg/g cream twice daily was continued. The patient had applied brimonidine 3 mg/g gel to the left side of her face on the morning of the visit to the clinic

in adults with rosacea, in a formulation of brimonidine 3 mg/g gel (MIRVASO®; Galderma International, La Défense, France) [10]. This agent has previously been shown to be an effective option in the treatment of moderate to severe erythema, with a good safety profile [9].

In December 2014, 2 months after commencing treatment with brimonidine 3 mg/g gel on the left side of her face and while continuing treatment with isotretinoin 10 mg once daily to maintain remission of inflammatory lesions, the patient returned to our department, showing mild erythema on the right side of the face, with background erythema cleared on the left side of the face (Fig. 1e). Of note, during the treatment period with brimonidine 3 mg/g gel, the patient did not experience any dermatological adverse events that required her to stop treatment temporarily.

At the most recent visit to our department in March 2015, the patient showed an increase in erythema severity on the right side of her face (not treated with brimonidine 3 mg/g gel) compared with the previous visit, reflecting the dynamic and changing nature of this symptom. The left side of the face, treated with brimonidine 3 mg/g gel on the morning of the visit to the clinic, remained clear of erythema (Fig. 1f). Isotretinoin treatment was stopped and the patient was advised to continue maintenance therapy with metronidazole 7.5 mg/g cream twice daily and brimonidine 3 mg/g gel.

3 Discussion and Evaluation

Here, we have reported the case of a patient with severe, inflamed PPR with a high inflammatory lesion count and severe erythema. Although corticosteroids are not generally recommended for the treatment of rosacea [6], because the level of inflammation in this patient was high, and similar to levels seen in patients with rosacea fulminans, it was decided that the initial course of treatment should consist of azithromycin 500 mg three times weekly in combination with prednisolone (initially 30 mg once daily and then gradually reduced and stopped). Following this short course of treatment, the next step was to continue decreasing the inflammation with isotretinoin 10 mg once daily monotherapy, and finally isotretinoin 10 mg once daily with brimonidine 3 mg/g gel on one side of the face to address the background erythema component of the disease.

In cases of recalcitrant PPR, oral isotretinoin can be used over a 3- to 4-month treatment period to achieve a complete clearance of inflammatory lesions [11]. In selected cases, a longer duration of therapy may be required in order to achieve an adequate level of improvement [11]. In this case, following 4 months

treatment with isotretinoin, all inflammatory lesions had disappeared. Treatment was continued for another 5 months to ensure maintained remission of inflammatory lesions.

As the skin permeability barrier is often impaired in rosacea, causing additional skin sensitivity and irritation [8], metronidazole 7.5 mg/g cream twice daily was applied throughout the courses of treatment, based on its proven effects in reducing skin irritation, transepidermal water loss, and erythema [12].

Based on the positive outcome seen overall, the patient is currently on maintenance therapy with metronidazole 7.5 mg/g cream twice daily and brimonidine 3 mg/g gel, with no relapse of disease.

4 Conclusions

In patients with very severe, inflamed rosacea, a multimodal, tailored approach with a short course of macrolide antibiotics in combination with corticosteroids is needed to strongly address the inflammatory component upfront and improve patient outcomes; corticosteroids are not strictly contraindicated in the treatment of rosacea if used for a short period to reduce inflammation showing signs of rosacea fulminans. In these patients, long-term therapy is needed to improve outcomes, with isotretinoin being effective in further reducing inflammatory lesions count and in maintaining remission.

The patient experienced a continuous reduction in the severity of her erythema, which was further improved with the use of brimonidine 3 mg/g. The lack of reported dermatological adverse events with this topical treatment could in part be due to the continued application of metronidazole; we believe metronidazole contributed to repairing and protecting the skin barrier, helping to restore skin barrier function and consequently lessening inflammation.

For complex cases such as this one, it has been acknowledged that careful selection and use of a combination of clinical treatments is essential to treat the individual. However, appropriate treatment recommendations and guidelines for such complex cases are still lacking. We believe that the publication of additional multifaceted cases such as the one presented here will help to facilitate the development of such guidelines.

Acknowledgments Editorial assistance in the preparation of the manuscript was provided by Dr. Raffaella Facchini and Dr. Carole Mongin-Bulewski of Havas Life Medicom. Support for this assistance was funded by Galderma. Sponsorship for article processing charges was funded by Galderma. Additional informed consent was obtained from the patient, for who identifying information is included in this article.

Authors' contributions MS and LG performed assessments of the patient. MS helped to draft the manuscript. Both authors read and approved the final manuscript.

Compliance with Ethical Standards

Professor Dr. Martin Schaller has been a member of advisory board panels over the past 2 years, and has received lecture fees from AbbVie, Bayer Healthcare, Galderma, Marpinion, and La Roche Posay. Dr. Lena Gonser declares that she has no conflicts of interest.

Open Access This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits any noncommercial use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

- Baldwin HE. Diagnosis and treatment of rosacea: state of the art. *J Drugs Dermatol*. 2012;11(6):725–30.
- Del Rosso JQ. Advances in understanding and managing rosacea: part 2: the central role, evaluation, and medical management of diffuse and persistent facial erythema of rosacea. *J Clin Aesthet Dermatol*. 2012;5(3):26–36.
- Torresani C. Clarithromycin: a new perspective in rosacea treatment. *Int J Dermatol*. 1998;37(5):347–9.
- Bakar O, Demircay Z, Gurbuz O. Therapeutic potential of azithromycin in rosacea. *Int J Dermatol*. 2004;43(2):151–4.
- Baldwin HE. Systemic therapy for rosacea. *Skin Therapy Lett*. 2007;12(2):1–9.
- Reinholz M, Tietze JK, Kilian K, Schaller M, Schofer H, Lehmann P, et al. Rosacea—S1 guideline [in English, German]. *J Dtsch Dermatol Ges*. 2013;11(8):768–80; 768–79. doi:10.1111/ddg.12101.
- Del Rosso JQ, Levin J. The clinical relevance of maintaining the functional integrity of the stratum corneum in both healthy and disease-affected skin. *J Clin Aesthet Dermatol*. 2011;4(9):22–42.
- Del Rosso JQ, Gallo RL, Kircik L, Thiboutot D, Baldwin HE, Cohen D. Why is rosacea considered to be an inflammatory disorder? The primary role, clinical relevance, and therapeutic correlations of abnormal innate immune response in rosacea-prone skin. *J Drugs Dermatol*. 2012;11(6):694–700.
- Fowler J, Jarratt M, Moore A, Meadows K, Pollack A, Steinhoff M, et al. Once-daily topical brimonidine tartrate gel 0.5 % is a novel treatment for moderate to severe facial erythema of rosacea: results of two multicentre, randomized and vehicle-controlled studies. *Br J Dermatol*. 2012;166(3):633–41. doi:10.1111/j.1365-2133.2011.10716.x.
- European Medicines Agency. MIRVASO®—Summary of product characteristics. February 2014. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002642/WC500163121.pdf. Accessed 31 Aug 2016.
- Park H, Del Rosso JQ. Use of oral isotretinoin in the management of rosacea. *J Clin Aesthet Dermatol*. 2011;4(9):54–61.
- Draeos ZD. Assessment of skin barrier function in rosacea patients with a novel 1 % metronidazole gel. *J Drugs Dermatol*. 2005;4(5):557–62.