Novel treatment (new drug/intervention; established drug/procedure in new situation)

Long-term effectiveness of dobesilate in the treatment of papulopustular rosacea

Pedro Cuevas,¹ Javier Angulo,¹ Guillermo Giménez-Gallego²

¹Research Department, Hospital Ramon y Cajal, Madrid, Spain;

²Estructura y Funcion de Proteinas, Centro de Investigaciones Biológicas, Madrid, Spain

Correspondence to Professor Pedro Cuevas, pedro.cuevas@hrc.es

Summary

This case report is a representative example from a study directed to assess the long-term clinical benefit of dobesilate in rosacea in five enrolled papulopustular rosacea patients with several years of disease, treated topically with 5% potassium dobesilate cream for 3 weeks. The patient suffered papulopustular rosacea for more than 10 years, during which she received topical metronidazole and azelaic acid, and systemic doxycycline therapies without satisfactory improvement. Dobesilate treatment promoted improvement of rosacea symptoms and signs. Two years after treatment the patient still shows a good facial cosmesis.

CASE PRESENTATION

A 43-year-old woman with papulopustular rosacea (figure 1A) applied twice daily a cream containing 5% potassium dobesilate for 3 weeks. The patient was evaluated at different times after treatment for rosacea symptoms and signs, including facial flushing, redness of the face, eruption of inflammatory papules and pustules on the

central face convexities. Three weeks of dobesilate treatment promoted marked improvement of rosacea. Episodes of flushing decreased in intensity and frequency and the inflammatory papules and pustules have cleared, although some less residual erythema persisted (figure 1B). Three weeks after treatment, flushing and residual erythema disappeared (figure 1C). As figure 1D,E shows the patient

Figure 1 Response to topical dobesilate treatment in a patient with papulopustular rosacea. This patient with papulopustular rosacea (A) applied dobesilate cream for 3 weeks, after which the inflammatory papules and pustules have cleared, although some residual erythema persisted (B). Three weeks after treatment residual erythema disappeared (C). At different times after treatment (6 months, (D) and 2 years, (E)) the patient showed an excellent facial cosmesis.

presented progressive and efficient improvement in facial cosmetic appearance.

TREATMENT

The local inhibition of fibroblast growth factor (FGF)/FGFR system that plays an important role in acne has an important clinical interest. This case report is the first demonstration of the long-term clinical efficacy of a specific and well-characterised FGF inhibitor topically used in papulopustular rosacea.

OUTCOME AND FOLLOW-UP

Three weeks of treatment cleared the inflammatory papules and pustules. Three weeks after treatment, residual erythema disappeared. After 2 years, the patient shows a good facial cosmesis.

DISCUSSION

Rosacea is a chronic inflammatory condition of the central face, eyelids and ocular surface, which cause facial disfigurement and vision-threatening keratoconjunctivitis despite therapeutic interventions.¹ Given the common occurrence of rosacea, a plethora of treatment has been promoted, yet recently, a rigorous review of treatment studies indicates that there was an urgent need for better quality, adequately designed trials on this topic.² An understanding of the basic mechanisms operating in rosacea is critical to that goal. Recently, rosacea has been considered as an angiogenesis-dependent disease in which FGF and vascular endothelial growth factor (VEGF) play an important pathophysiological role.^{3–5} Previously, we have reported that topical application of dobesilate, a specific and well-characterised FGF inhibitor⁶ shows clinical efficacy in erythematotelangiectatic rosacea variety.³ Here, we report a long-term efficacy of topical dobesilate in papulopustular rosacea clinical variant. FGF and its receptors (FGFR) signal pathways play a central role in the function and homeostasis of the sebaceous glands, and clinical and experimental data support a role of disturbed FGF/FGFR signals in comedogenesis. Activation of FGF/FGFR system leads to proliferation of perifollicular fibroblasts, infundibular keratinocytes and sebocytes, cellular hallmarks of acne.^{7–9} Furthermore, recent clinical and preclinical observations have clearly shown that known antiacne agents attenuate FGF/FGFR signalling as a common, but unspecific, mode of action.¹⁰ Relevance of the inhibition of FGF/FGFR system for treating papulopustular rosacea is further stressed by the data reported here, using a specific inhibitor of this signalling system. It should be also taken into account that,

being FGF a necessary mediator of VEGF activity,⁶ dobesilate also inhibits this last signalling system, as it has been also recently described.¹¹ The case report presented here is a representative example of five enrolled rosacea patients from a study directed to assess the long-term clinical benefit of dobesilate in rosacea. Taken together these data support a new therapeutic modality for a safe and efficient topical treatment of rosacea.

Learning points

- Rosacea is an angiogenesis-dependent disease.
- FGF and VEGF are involved in rosacea pathophysiology.
- Dobesilate inhibits FGF and VEGF signalling.
- Topical dobesilate improved clinical manifestations of papulopustular rosacea.
- No adverse effects associated with the treatment were observed.

Acknowledgements This work was supported by CONSOLIDER CSD2009-00088 from the Spanish Ministry of Science and Innovation, and by Action Medicines S.L.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Powell FC.** Clinical practice. Rosacea. *N Engl J Med* 2005;**352**:793–803.
2. **van Zuuren EJ,** Graber MA, Hollis S, *et al.* Interventions for rosacea. *Cochrane Database Syst Rev* 2005;**3**:CD003262.
3. **Cuevas P,** Arrazola JM. Therapeutic response of rosacea to dobesilate. *Eur J Med Res* 2005;**10**:454–6.
4. **Smith JR,** Lanier VB, Brazier RM, *et al.* Expression of vascular endothelial growth factor and its receptors in rosacea. *Br J Ophthalmol* 2007;**91**:226–9.
5. **Aroni K,** Tsagrani E, Kavantzis N, *et al.* A study of the pathogenesis of rosacea: how angiogenesis and mast cells may participate in a complex multifactorial process. *Arch Dermatol Res* 2008;**300**:125–31.
6. **Fernández IS,** Cuevas P, Angulo J, *et al.* Gentisic acid, a compound associated with plant defense and a metabolite of aspirin, heads a new class of *in vivo* fibroblast growth factor inhibitors. *J Biol Chem* 2010;**285**:11714–29.
7. **Zouboulis CC,** Eady A, Philpott M, *et al.* What is the pathogenesis of acne? *Exp Dermatol* 2005;**14**:143–52.
8. **Melnik B,** Schmitz G. FGFR2 signaling and the pathogenesis of acne. *J Dtsch Dermatol Ges* 2008;**6**:721–8.
9. **Melnik BC.** Role of FGFR2-signaling in the pathogenesis of acne. *Dermatoendocrinol* 2009;**1**:141–56.
10. **Melnik BC,** Schmitz G, Zouboulis CC. Anti-acne agents attenuate FGFR2 signal transduction in acne. *J Invest Dermatol* 2009;**129**:1868–77.
11. **Angulo J,** Peiró C, Romacho T, *et al.* Inhibition of vascular endothelial growth factor (VEGF)-induced endothelial proliferation, arterial relaxation, vascular permeability and angiogenesis by dobesilate. *Eur J Pharmacol* 2011;**667**:153–9.

This pdf has been created automatically from the final edited text and images.

Copyright 2011 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Cuevas P, Angulo J, Giménez-Gallego G. Long-term effectiveness of dobesilate in the treatment of papulopustular rosacea. *BMJ Case Reports* 2011;10.1136/bcr.08.2011.4579, date of publication

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow