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Noteworthy Paper

Calcitonin gene-related peptide inhibition: the advent of biologics in rosacea

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Rosacea is a chronic inflammatory dermatosis, characterized by central facial erythema, which is often accompanied by facial flushing, skin sensitivity, papules and pustules, among other features. Despite advancements in medical treatments and patient adherence, persistent flushing and erythema remain challenging to treat.[1]

A 2024 study by Wienholtz *et al.*[2] represents a promising development in addressing refractory flushing associated with rosacea. It investigated the use of erenumab, a monoclonal antibody (mAb) that targets the calcitonin gene-related peptide (CGRP) receptor, for patients with treatment-resistant erythema and flushing. Although primarily indicated for migraine prophylaxis, the use of erenumab in this context stems from the growing understanding of neurovascular mechanisms in the pathogenesis of rosacea.[2]

This single-group, open-label, nonrandomized controlled trial enrolled 30 adults with moderate-to-extreme flushing and/or moderate-to-severe erythema on 15 or more days per month. The majority of the participants (87%) had not responded to at least one prior rosacea therapy and 43% had failed three or more previous treatments. Participants received erenumab 140 mg subcutaneously every 4 weeks for 12 weeks. No other rosacea treatments were permitted during the study period. Outcomes were tracked using daily electronic diaries, clinician assessments and quality-of-life measures.

The primary endpoint was the change in the number of days with moderate-to-extreme flushing from baseline to weeks 9–12, which significantly reduced by 6.9 days per month (95% CI –10.4 to –3.4; $P<0.001$). Similarly, the number of days with moderate-to-severe erythema decreased by 8.1 days (95% CI –12.5 to –3.7; $P<0.001$). Nearly one-quarter of patients achieved ≥50% reduction in flushing, and over half achieved ≥50% reduction in erythema by week 12.

Subgroup analyses revealed that, among patients with ≥10 days per month of severe-to-extreme flushing at baseline, the average dropped from 20.8 to 3.8 days, an 81% improvement. Improvements in facial redness, measured by patient and clinician assessments, were observed and sustained even 12 weeks after the final dose.

Quality of life, assessed by the Dermatology Life Quality and Rosacea Quality of Life indices, showed significant improvement. Although mood or anxiety scores showed no meaningful changes, the trend suggests that cosmetic and social concerns linked to visible flushing may improve with symptom relief.

Erenumab's safety profile was reassuring and consistent with prior data from migraine studies. Common adverse events were constipation (33%) and transient worsening of flushing post-infection (13%). One participant withdrew because of an unrelated serious adverse event (gallstones) and two discontinued for logistical reasons. While the results are promising, the study's open-label, nonrandomized design and lack of a placebo control limit the generalizability of the findings. The short follow-up period of 12 weeks and absence of data collection at the last dose also restrict conclusions about long-term efficacy and safety.

CGRP is a potent neuropeptide vasodilator produced in the central and peripheral nervous systems. Although the pathophysiology of rosacea is not completely understood, it has been found that intravenous CGRP infusion causes flushing and might be associated with stinging sensations in rosacea.[4] In addition to CGRP, compounds such as substance P, transient receptor potential and vasoactive intestinal peptide have shown elevated levels of proinflammatory cytokines and chemokines in rosacea.[5] Pituitary adenylate cyclase-activating polypeptide-38 has also been shown to cause flushing and oedema.[2] Rosacea and migraines have common stressors such as emotional stress, ultraviolet radiation exposure and certain foods and drinks. This may suggest pathophysiological similarities and may provide a rationale for CGRP being an effective treatment for erythema and flushing in rosacea.[4] The association and proposed shared pathophysiology between rosacea and migraine have also previously been discussed in a meta-analysis, supporting a potential link between the two conditions.[3] Apart from rosacea, CGRP has also been shown to play a role in other dermatological conditions such as psoriasis, atopic dermatitis, contact dermatitis and candidiasis.[5] A 2023 study by Sia *et al.* investigated the use of

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CGRP mAbs (galcanezumab, erenumab, fremanezumab) in 13 patients with rosacea. Approximately 54% of patients experienced improvement in both papules/pustules and erythema/flushing. Only three participants reported mild injection-site reactions.[6] These findings offer further support for CGRP-targeted therapies as a rational approach for treatment.

Together, these studies provide evidence supporting the role of CGRP receptor inhibition as a therapeutic approach for persistent flushing and erythema in rosacea. While erenumab is not currently licensed for dermatological use, these findings highlight neurovascular mechanisms in rosacea pathogenesis and open avenues for targeted treatment. Larger, randomized, placebo-controlled studies are required to validate these results, to identify optimal patient populations and to assess long-term safety and efficacy of CGRP-targeted therapies. The work of Wienholtz *et al*.[2] is an important step toward redefining treatment strategies for rosacea.

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Conflicts of interest

F.R.A. has received honoraria, sponsorship and speaker fees from L'Oreal, Galderma, Novartis, Leo Pharma, Incyte and Eli Lilly. The other authors declare no conflicts of interest.

Data availability

No new data were collected for this publication.

Ethics statement

Not applicable.

Patient consent

Not applicable.

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CPD questions

Learning objective

To consolidate knowledge of the study investigating erenumab as a treatment for refractory flushing and erythema in rosacea.

Question 1

What dose of erenumab was used for treating rosacea in the study by Wienholtz *et al*.?

(a) 70 mg once weekly.
(b) 70 mg once every 4 weeks.
(c) 140 mg once weekly.
(d) 140 mg once every 4 weeks.
(e) 280 mg once every 4 weeks.

Question 2

What is the most frequently reported adverse effect from erenumab?

(a) Agranulocytosis.
(b) Conjunctivitis.
(c) Constipation.
(d) Headache.
(e) Postural hypotension.

Instructions for answering questions

This learning activity is freely available online at https://oupce.rievent.com/a/PTCOTS

Users are encouraged to

- Read the article in print or online, paying particular attention to the learning points and any author conflict of interest disclosures.
- Reflect on the article.
- Register or login online at https://oupce.rievent.com/a/PTCOTS and answer the CPD questions.
- Complete the required evaluation component of the activity.

Once the test is passed, you will receive a certificate and the learning activity can be added to your RCP CPD diary as a self-certified entry.

This activity will be available for CPD credit for 5 years following its publication date. At that time, it will be reviewed and potentially updated and extended for an additional period.