Calcitonin Gene-Related Peptide Inhibition: The Advent of Biologics in Rosacea

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

A recent study by Wienholtz et al., published in *JAMA Dermatology* (2024), 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, erenumab's use in this context stems from the growing understanding of neurovascular mechanisms in the pathogenesis of rosacea [2].

This single-group, open-label, non randomised controlled trial enrolled 30 adults with moderate-to-extreme flushing and/or moderate-to-severe erythema on ≥15 days per month. 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 140 mg of erenumab 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; $p < .001$). Similarly, the number of days with moderate-to-severe erythema decreased by 8.1 days (95% CI –12.5 to –3.7; $p < .001$). 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 amongst patients with ≥10 days per month of severe-to-extreme flushing at baseline, the average dropped from 20.8 to 3.8 days, showing 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 Index (DLQI) and the Rosacea Quality of Life (RosaQoL) index, 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 due to an unrelated serious adverse event (gallstones), and two discontinued for logistical reasons. While the results are promising, the study's open-label, non randomised design and lack of a placebo control limit the generalisability 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 was 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 (SP), transient receptor potential (TRP), and vasoactive intestinal peptide (VIP) have shown elevated levels of pro-inflammatory cytokines and chemokines in rosacea [5]. Pituitary adenylate cyclase-activating polypeptide-38 (PACAP38) has also been shown to cause flushing and oedema [2]. Rosacea and migraines have common stressors like emotional stress, ultraviolet radiation exposure, certain foods, and drinks. This may suggest pathophysiological similarities and provide rationale for CGRP being an effective treatment for erythema and flushing in rosacea [4]. The association and proposed shared

pathophysiology between rosacea and migraine has 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 like psoriasis, atopic dermatitis, contact dermatitis, and candidiasis [5]. A prior study by Sia et al., 2023 investigated the use of CGRP MAbs (galcanezumab, erenumab, fremanezumab) in 13 rosacea patients. Approximately 54% of patients experienced improvement in both papules/pustules and erythema/flushing. Only 3 participants reported mild injection-site reactions [6]. These offer further support for CGRP-targeted therapies as a rational approach for treatment.

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

References

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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 in the study for treating rosacea?

(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 was the most frequently reported side effect from erenumab?

(a) Agranulocytosis

(b) Conjunctivitis

(c) Constipation

(d) Headache

(e) Postural hypotension