Rimegepant

A new oral migraine medication

SHULI CHENG MB BS(Hons), FRACP; **JASON C. RAY** MB BS, FRACP
TAMSIN HILLARD MB BS; **RICHARD J. STARK** MB BS, FRACP, MACLM

Migraine is common and can be disabling. Calcitonin-gene related peptide (CGRP) blocking agents are effective in treating migraine. Rimegepant is the first oral CGRP antagonist available in Australia.

KEY POINTS

- Migraine is the most common neurological disease worldwide.
- Calcitonin-gene related peptide (CGRP) blockers, comprising of monoclonal antibodies and oral antagonists, are disease-specific therapies for migraine.
- Three CGRP monoclonal antibodies are available on the PBS for chronic migraine prophylaxis; however, these are not suitable for acute treatment.
- Rimegepant, the first in a new class of CGRP blockers, is available as an oral tablet that is indicated for both acute and prophylactic migraine treatment in adults. It is not currently PBS listed.

Migraine is the most common neurological disease worldwide and is the second leading cause of disability in people under the age of 50 years.[1] A personalised management approach is vital for the care of people who experience migraines. The authors have previously described a migraine management framework in 2022.[2] This article describes a newly available calcitonin-gene related peptide (CGRP) blocker rimegepant for the management of migraine.

What are calcitonin-gene related peptide blocking treatments?

CGRP is a neuropeptide that is expressed widely throughout the body, including in trigeminal neurons. Through the trigeminocervical system, CGRP has been implicated in the generation of pain in migraine.[3] Several CGRP monoclonal antibodies and oral antagonists have been developed to block the action of CGRP as treatments for migraine. These are considered disease-specific treatments.

Three CGRP monoclonal antibodies are available on the PBS as prophylaxis for chronic migraine: galcanezumab, fremanezumab and eptinezumab. These monoclonal antibodies bind to the CGRP ligand and block the action of CGRP. Because of their long half-lives (between 27 and 31 days), they are ideal for prophylaxis but not for acute treatment. These treatments became available in Australia in 2021 and the authors have discussed their efficacy, safety and precautions in a previous article.[4]

With CGRP antibodies now well established in Australia, we welcome the arrival of the small molecule CGRP antagonists (gepants), which can be taken orally. This new formulation will provide the option of a migraine-specific CGRP blocker both to treat acute migraine and as a migraine prophylaxis.

What is rimegepant?

Rimegepant is an oral CGRP blocker that is now approved by the TGA. It is currently available as an oral disintegrating tablet (ODT) containing 75mg rimegepant that can be taken with or without meals sublingually and will disintegrate in the mouth without liquid.

When and in whom is rimegepant used?

For acute treatment of migraine (with and without aura), rimegepant 75mg is used at the onset of a migraine attack, with a maximum dose of 75mg (one tablet) in a 24-hour period. In a phase 3 clinical

MedicineToday 2024; 25(1-2): 35-37

Dr Cheng is a Neurologist in the Department of Neurology, Alfred Health, Melbourne.
Dr Ray is a Neurologist in the Department of Neurology, Alfred Health and Department of Neurology, Austin Health; and a Research Fellow in the Department of Neurosciences, Monash University, Melbourne.
Dr Hillard is a Headache Fellow in the Department of Neurology, Alfred Health; and a Masters by Research Candidate in the Department of Neurosciences, Monash University, Melbourne.
Professor Stark is a Neurologist in the Department of Neurology, Alfred Health, Melbourne; and Adjunct Clinical Professor in the Department of Neurosciences, Monash University, Melbourne, Vic.

trial of patients with a history of migraine of at least one year, the acute treatment coprimary endpoint for rimegepant was superior to placebo at two hours postdose for: freedom from pain (21% *vs* 11%, respectively; p<0.0001), freedom from most bothersome symptoms (35% *vs* 27%, respectively; p=0.0009) and the percentage of participants with pain relief (60% *vs* 40%, respectively; p<0.0001).[5] It is possible that the ODT formulation could help with the rapid onset of relief and with early nausea.

For migraine prophylaxis, the recommended dose is 75 mg every other day. In a phase 2/3 clinical trial of adults with a history of migraine of at least one year, oral rimegepant 75 mg administered every other day was superior to placebo on the primary endpoint of change in the mean number of migraine days per month during weeks 9 to 12, with a change of –4.3 days with rimegepant compared with –3.5 days with placebo (p=0.0099). The 50% responder rate was 49% for rimegepant and 41% for placebo (p=0.044).[6] If rimegepant is also used for acute treatment, the recommendation is to not exceed the total dose of 75 mg rimegepant in a 24-hour period.

Rimegepant is currently recommended for patients aged 18 years and older. A phase 3 clinical trial to test the efficacy and safety of rimegepant in children and adolescents aged 6 to 18 years is currently under way (Clinical trial ID NCT05156398).

How is rimegepant used?

The primary use for rimegepant is as a stand-alone acute treatment or as migraine prophylaxis. The clinical scenarios likely to be encountered for the use of rimegepant are as an acute treatment in patients already receiving a CGRP monoclonal antibody and the concomitant use of rimegepant and a triptan.

Patients on CGRP monoclonal antibodies were excluded from the initial rimegepant clinical trials. In a cohort study of 13 patients, the combination of rimegepant and CGRP monoclonal antibodies was well tolerated over a mean treatment duration of 9.6 weeks. Adverse events other than nasopharyngitis were reported by individual patients and were of mild or moderate severity.[7] The efficacy of gepants in this context suggests that not all CGRP signalling is blocked by the longer-acting CGRP monoclonal antibodies.

To assess the safety of concurrent administration of gepants and triptans, sequential and concomitant use of subcutaneous sumatriptan and oral rimegepant was studied in 42 healthy young adults (between 18 and 50 years of age). Concurrent administration did not increase blood pressure or change the pharmacokinetics of each drug and was relatively well tolerated by patients.[8] Studies of combination use are small; therefore, ongoing studies including real-world data are required.

Common side effects

The most common adverse event of rimegepant use for acute treatment was nausea (2% in rimegepant group, <1% in placebo group), with no serious adverse events reported.[5] For migraine prophylaxis, tolerability was similar in both treatment and placebo groups. Adverse events occurred in at least 2% of participants in the rimegepant group and included nasopharyngitis (4%), nausea (3%), urinary tract infection (2%) and upper respiratory tract infection (2%).[6] As with all new therapies, clinicians should be alert to any potential newly recognised side effects and should report any suspected adverse events to the TGA (www.tga.gov.au/reporting-problems).

Important precautions and interactions

No dose adjustments for rimegepant are required for patients with mild to moderate renal or hepatic impairment. There is no experience of rimegepant use in patients with end-stage renal disease, those who are undergoing dialysis or those with severe hepatic impairment.

Given that CGRP is expressed widely throughout the body, clinicians should be cautious about the use of CGRP-blocking treatments in patients with severe constipation, hypertension, Raynaud's disease or active vascular disease.[3]

Rimegepant is a substrate of CYP3A4 and CY2CP, P-glycoprotein and BCRP efflux transporters. Its metabolism might be impacted by CYP3A4 inducers and inhibitors, such as verapamil, erthyromycin, diltiazem and azole antifungals.

There is limited experience of CGRP-blocking treatments in pregnancy and breastfeeding and they are currently not recommended as an option during pregnancy and lactation.

How will rimegepant be used in practice?

As it is not PBS listed, rimegepant will be more expensive than current standard treatment options, which may limit its use for patients with migraine.

When might rimegepant be used over a triptan for acute treatment of migraine?

Although no head-to-head comparisons between triptans and gepants exist, the efficacy of the two classes is about the same (perhaps marginally in favour of triptans). However, individual patients may respond better to one medication over the other. Rimegepant may be preferred over a triptan:

- if triptan use is limited by side effects, such as chest tightness or lethargy
- if triptan use has been ineffective
- if triptan overuse results in medication overuse headaches, as some data suggest that gepants are less likely to produce these than triptans.[9]

Rimegepant may also be used concomitantly in patients already taking CGRP antibodies or a triptan.

When might rimegepant be used over a CGRP antibody for migraine prophylaxis?

Rimegepant may be preferred over a CGRP antibody in the following scenarios:

- for patients who are needle phobic
- in women considering a pregnancy to reduce the time off medication. The current advice for patients planning pregnancy is to be off such medications for at least five half-lives before beginning a pregnancy. For patients taking CGRP antibodies, this equates to about five months, but would only be about two weeks for a patient taking gepants
- as a short course around the time of menstruation to prevent menstrual migraine, although this strategy has not yet been proven effective
- as a short course for bridging therapy in cases of medication overuse; however, this strategy has not yet been proven effective.

Conclusion

Rimegepant is now available for use in adults with migraine with aura or migraine without aura. It is a welcome addition to the available options both for acute treatment and for prophylaxis. Currently, cost will limit its use but this may change if it becomes available with PBS subsidy. MT

References

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018; 392: 1789-1758.
2. Hillard T, Ray JC, Hutton E, Stark RJ. Migraine in 2022: an update on management. Med Today 2022; 23(9): 57-64.
3. Ray JC, Kapoor M, Stark RJ, et al. Calcitonin gene related peptide in migraine: current therapeutics, future implications and potential off target effects. J Neurol Neurosurg Psychiatry 2021; 92: 1325-1334.
4. Ray JC, Hutton EJ, Cheng S, Zhang L, Stark RJ. New horizons in migraine therapy: CGRP monoclonal antibodies. Med Today 2021; 22(6): 61-64.
5. Croop R, Goadsby PJ, Stock DA, et al. Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: a randomised, phase 3, double-blind, placebo-controlled trial. Lancet 2019; 394: 737-745.
6. Croop R, Lipton RB, Kudrow D, et al. Oral rimegepant for preventive treatment of migraine: a phase 2/3 randomised, double-blind, placebo-controlled trial. Lancet 2021; 397: 51-60.
7. Berman G, Croop R, Kudrow D, et al. Safety of rimegepant, an oral CGRP receptor antagonist, plus CGRP monoclonal antibodies for migraine. Headache 2020; 60: 1734-1742.
8. Croop R, Ivans A, Anderson MS, et al. A phase 1 randomized study of hemodynamic effects and pharmacokinetic interactions during concomitant use of rimegepant and sumatriptan in healthy adults. Cephalalgia reports 2021; 4: 1-4.
9. Holland PR, Saengjaroentham C, Sureda-Gibert P, Strother L. Medication overuse headache: divergent effects of new acute antimigraine drugs. Cephalalgia 2020; 40: 889-891.

COMPETING INTERESTS: Dr Hillard: None. Dr Cheng has received support for attending meetings from Abbvie and is a Committee Member of the Australia New Zealand Headache Society. Dr Ray has received payment for consultation and lectures from Abbvie, Novartis and Viatris; support for attending meetings from Pfizer; and is on the Advisory Boards for Lilly, Pfizer and Viatris. Professor Stark has received payment for consultation and lectures from Abbvie, Eli Lilly, Lundbeck, Pfizer and Teva; travel support from Abbvie; was the immediate past President of the Australia and New Zealand Headache Society; and Treasurer and Trustee (2015–2023) of the World Federation of Neurology.