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Research Article

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Real-world outcomes associated with initial oral CGRP receptor antagonist integration strategies in children and adolescents with migraine: a multicenter cohort study

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Abstract

Background: Evidence on how oral calcitonin gene-related peptide (CGRP) receptor antagonists can be integrated into preventive treatment strategies for children and adolescents with migraine remains limited. We evaluated real-world outcomes associated with different initial strategies for incorporating rimegepant into ongoing preventive management.

Methods: We conducted a retrospective multicenter cohort study using data from the China Headache and Vertigo Registry System. Patients aged ≤18 years were classified by initial treatment strategy: conventional preventive therapy without rimegepant integration, conventional preventive therapy plus regular rimegepant integration, or conventional preventive therapy plus acute-on-demand rimegepant integration. The primary outcome was a ≥50% reduction in monthly headache days (MHDs) at 4 months; a ≥75% reduction was secondary. Covariate-balancing propensity score–based overlap weighting using six prespecified covariates was combined with doubly robust outcome regression. Treatment trajectories and documented adverse events were summarized descriptively.

Results: Among 109 patients, 23 received conventional preventive therapy alone, 64 plus regular rimegepant integration, and 22 plus acute-on-demand integration. Adjusted probabilities of achieving ≥50% MHD reduction were 51.2%, 67.5%, and 78.6%, respectively. Compared with conventional therapy alone, adjusted risk differences were 16.3 percentage points (95% CI, −8.8 to 41.4) for plus regular integration and 27.4 percentage points (95% CI, −1.4 to 56.2) for plus acute-on-demand integration; neither comparison reached statistical significance. For ≥75% response, adjusted probabilities were 37.2%, 60.4%, and 76.6%, with corresponding risk differences of 23.2 percentage points (95% CI, 2.0–44.4) and 39.4 percentage points (95% CI, 12.7–66.1). Among patients initiating plus regular rimegepant integration, subsequent trajectories included continued regular integration, transition to acute-on-demand integration, and discontinuation for heterogeneous reasons. Few

adverse events were documented; one patient discontinued because of nausea, and no serious adverse events were documented.

Conclusions: Rimegepant-adding strategies showed numerically higher adjusted probabilities of the primary ≥50% response, although primary comparisons remained statistically uncertain. More pronounced associations were observed for the secondary ≥75% response. These findings are preliminary and hypothesis-generating and support prospective evaluation of how oral CGRP receptor antagonists may be integrated into pediatric migraine prevention.

Keywords: pediatric migraine; adolescent migraine; CGRP receptor antagonist; rimegepant; preventive treatment; real-world evidence; treatment strategy

Background

Migraine is a common and disabling neurological disorder in children and adolescents and contributes substantially to neurological disease burden [1]. Beyond headache symptoms, pediatric migraine can impair school functioning and health-related quality of life [2-4]. Preventive treatment should be considered when attacks are sufficiently frequent or severe to cause clinically meaningful disability, particularly when optimized acute treatment is inadequate or required too frequently[2-4]. However, treatment selection in younger patients remains challenging because the evidence base for many preventive therapies is less extensive than in adults and treatment response and tolerability vary considerably across individuals[2, 5].

Calcitonin gene-related peptide (CGRP)-targeted therapies have expanded migraine treatment options. Rimegepant, an oral CGRP receptor antagonist, is effective for both acute and preventive treatment in adults [6-8]. Pediatric evidence is emerging: randomized data support fremanezumab in children and adolescents with episodic migraine [9], while real-world studies have described CGRP-targeted treatment in adolescents and young adults [10, 11]. These findings support the expanding role of CGRP-targeted therapy in younger populations, although much of the available evidence has focused on monoclonal antibodies or CGRP-targeted therapies as a broad treatment class rather than on oral gepant treatment strategies.

More recently, a multicenter pediatric chart review described preventive use of rimegepant and atogepant [12], a retrospective study reported acute rimegepant use in adolescents [13], and a phase 1 study provided pediatric pharmacokinetic and tolerability data for weight-adjusted rimegepant dosing [14]. A phase 3 preventive trial of rimegepant in patients aged 6 to <18 years is ongoing (NCT05156398). Collectively, these studies establish an emerging evidence base for pediatric rimegepant use but address distinct questions of pharmacokinetics, tolerability, acute treatment, or preventive use. Evidence remains limited on how rimegepant is

incorporated into ongoing preventive regimens in routine practice and whether different utilization strategies are associated with different clinical outcomes.

Recent real-world evidence further illustrates this gap. In PRIME-Teen, adolescents with high-burden migraine contributed sequential treatment episodes involving conventional oral preventives and CGRP monoclonal antibodies; CGRP monoclonal antibody episodes were associated with greater treatment persistence and more favorable migraine outcomes. Given its retrospective, non-randomized, sequential design, the findings were appropriately considered hypothesis-generating rather than evidence of comparative effectiveness[15]. In China, prospective multicenter real-world evidence has also described acute and preventive rimegepant use in adults [16]. However, these studies did not specifically compare alternative strategies for incorporating an oral CGRP receptor antagonist into pediatric preventive care.

Rimegepant is particularly relevant to this question because it can be used for both acute and preventive treatment in adults. In pediatric real-world practice, patients receiving conventional preventive therapy may add rimegepant either regularly as an additional preventive component or acutely on demand while continuing background prevention. This dual-use characteristic creates a clinically relevant treatment-strategy question that cannot be captured by a simple rimegepant-versus-no-rimegepant comparison.

Real-world comparisons of such strategies are susceptible to confounding by indication because disease burden, previous treatment exposure, comorbidity, and clinician or family preferences may influence treatment assignment. Generalized overlap weighting provides a framework for balancing measured baseline covariates across multiple treatment groups while focusing inference on patients with clinical overlap among the available strategies[17, 18]. Combined with an adjusted outcome model, this approach can improve robustness to model misspecification, although residual and unmeasured confounding remain possible[19].

Using data from the China Headache and Vertigo Registry System (CHRS), we therefore compared three initial treatment strategies among children and adolescents with migraine: conventional preventive therapy without rimegepant integration, conventional preventive therapy plus regular rimegepant integration, and conventional preventive therapy plus acute-on-demand rimegepant integration. The primary objective was to compare the probability of achieving a ≥50% reduction in monthly headache days (MHDs) at 4 months. Secondary analyses evaluated ≥75% response, treatment trajectories, documented adverse events, and exploratory differences by migraine phenotype and vestibular migraine status. This study provides a multicenter real-world comparison of alternative initial strategies for integrating rimegepant into preventive migraine management in children and adolescents in China.

Study design and data source

This multicenter retrospective real-world cohort study was conducted using data from CHRS registry platform which was registered with ClinicalTrials.gov (NCT04939922; first posted on June 14, 2021). The CHRS is an ongoing nationwide registry established to systematically collect standardized longitudinal clinical information from patients with headache and vestibular disorders. The CHRS currently includes 188 participating medical centers across China. Although most participating centers primarily provide adult neurological care, children and adolescent patients were also enrolled at 40 registered centers where pediatric headache care was available.

All patients included in this study were selected and diagnosed with migraine by headache specialists according to the International Classification of Headache Disorders, third edition (ICHD-3), and were considered candidates for preventive migraine therapy based on clinical evaluation. Treatment decisions were made by treating physicians according to headache burden, previous treatment response, clinical characteristics, and patient/family preferences.

The study entry date was defined as the initiation date of the initial preventive treatment strategy after rimegepant became available within the participating centers in May 2025. Although the present analysis was retrospective, follow-up information was prospectively collected within the CHRS registry framework. Daily headache information was recorded using standardized headache diaries, and treatment effectiveness was assessed through headache diaries and clinical follow-up records. When necessary, additional telephone follow-up was conducted by clinicians to clarify incomplete clinical information.

Study population

Patients aged ≤18 years registered in the CHRS between May 30, 2025, and February 2026 were screened. Eligible patients met all of the following criteria: age ≤ 18 years at initiation of preventive treatment; physician-confirmed diagnosis of migraine according to ICHD-3 criteria; initiation of pharmacological preventive treatment; complete baseline clinical information available; completion of at least 4 months of follow-up. Patients were excluded if they had: secondary headache disorders; incomplete baseline information, including headache diaries and critical clinical characteristics such as MHDs, headache course, preventive strategy, etc. missing follow-up outcome assessment; primary treatment with non-pharmacological interventions; rimegepant monotherapy as preventive treatment.

Baseline characteristics were collected at the initial clinical visit by trained research coordinators using standardized semi-structured questionnaires within the CHRS platform. Variables included demographic characteristics (age, sex), headache characteristics (baseline MHDs, headache duration, migraine phenotype such as episodic migraine versus chronic migraine, migraine with aura, and vestibular migraine), migraine-related comorbidities (motion sickness history, headache family history), previous treatment history (previous preventive medications, previous

analgesics), baseline treatment medications (concomitant flunarizine use, concomitant antiepileptic medication use, concomitant antidepressant use), and available standardized clinical assessments.

Additional clinical scales collected when available included the Migraine Disability Assessment Scale (MIDAS), the Headache Impact Test-6 (HIT-6), the Generalized Anxiety Disorder Scale-7 (GAD-7), the Patient Health Questionnaire-9 (PHQ-9), the Pittsburgh Sleep Quality Index (PSQI).

Initial preventive treatment strategies

All included patients were considered candidates for pharmacological migraine prevention. Conventional preventive medication constituted the background preventive-treatment approach. Patients were classified according to the initial treatment strategy at study entry into three groups:

Conventional preventive therapy without rimegepant integration: Patients received conventional preventive medications without rimegepant as part of the preventive strategy. Conventional preventive therapies included agents such as flunarizine, antiepileptic medications, and antidepressants. Patients in this group could receive non-CGRP acute migraine treatments during follow-up when clinically indicated.

Conventional preventive therapy plus regular rimegepant integration: Patients received conventional preventive therapy combined with regularly scheduled rimegepant as an adjunctive preventive strategy. Rimegepant orally disintegrating tablets were prescribed every other day according to clinical practice.

Conventional preventive therapy plus acute-on-demand rimegepant integration: Patients received conventional preventive therapy and used rimegepant orally

disintegrating tablets for acute migraine attacks as part of the overall treatment strategy.

Patients receiving rimegepant monotherapy for prevention were excluded because the study was designed to evaluate rimegepant as an adjunct to conventional preventive therapy.

Treatment-group classification was determined at study entry and was not redefined by subsequent treatment modification, including discontinuation of regular rimegepant integration, transition to acute-on-demand integration, or addition or modification of other preventive medications. Effectiveness analyses therefore followed the initial treatment-strategy classification throughout follow-up.

Outcomes

Primary effectiveness outcome

The primary effectiveness outcome was the proportion of patients achieving a ≥ 50% reduction in MHDs [20-22] from baseline after 4 months of treatment. MHDs were derived from standardized headache diaries and defined as the number of calendar days with headache occurrence within a 24-hour period.

Secondary effectiveness outcome

The secondary effectiveness outcome was the proportion of patients achieving a ≥ 75% reduction in MHDs at 4 months. This more stringent responder threshold was used to characterize patients experiencing a deeper level of clinical improvement beyond the conventional ≥50% response definition [23, 24].

Rimegepant treatment trajectories following regular rimegepant initiation

Treatment trajectories were descriptively evaluated among patients initially receiving regular rimegepant integration and were categorized as: continued regular rimegepant

integration; transition to acute-on-demand rimegepant integration; or discontinuation of rimegepant integration.

Reasons for treatment continuation, modification, or discontinuation were obtained from clinical documentation and follow-up records.

Because post-baseline treatment modifications may reflect clinical improvement, insufficient effectiveness, tolerability, patient or family preference, or other real-world considerations, treatment trajectory analyses were considered descriptive outcomes and were not used to redefine the initial treatment exposure or as comparative effectiveness endpoints.

Documented adverse events

Adverse events documented during clinical follow-up were identified from medical records and follow-up documentation and summarized descriptively. Because adverse-event ascertainment was based on routine clinical documentation, safety analyses were considered descriptive and were not designed to establish the incidence of rare or delayed adverse events.

Covariate selection and confounding adjustment

Because treatment allocation was not randomized, potential baseline differences between treatment groups were expected. Candidate baseline variables were initially considered based on clinical relevance and previous evidence regarding factors potentially associated with treatment selection or migraine outcomes.

To reduce model instability in this relatively small observational cohort, the final adjustment set was prespecified based on clinical knowledge and a directed acyclic graph-informed approach.

The six prespecified baseline covariates included: age category (age class), baseline MHDs, headache duration, migraine phenotype (episodic versus chronic migraine), baseline preventive medication burden and previous analgesic use. The same prespecified covariate set was used in the treatment-assignment and outcome-regression models.

Statistical analysis

Baseline characteristics were summarized using descriptive statistics. Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range [IQR]), as appropriate, and categorical variables as frequencies and percentages.

Covariate balancing propensity score overlap weighting

Potential confounding arising from measured baseline differences among the three initial treatment strategies was addressed using covariate-balancing propensity score (CBPS)-based overlap weighting [25].

The CBPS approach incorporates covariate balance directly into propensity score estimation. Generalized overlap weighting[17, 18] was selected to reduce the influence of observations with extreme treatment probabilities and to emphasize patients with greater clinical overlap among three treatment strategies. The resulting estimand corresponds to the average treatment effect in the overlap population (ATO).

Covariate balance after weighting was assessed using standardized mean differences (SMDs), with an absolute SMD < 0.10 considered indicative of adequate balance. Effective sample sizes were additionally examined to evaluate the information retained after weighting.

Covariate-adjusted weighted outcome modeling

After application of CBPS-based overlap weights, weighted logistic regression models were fitted for the ≥50% and ≥75% response outcomes. Under standard assumptions, this approach provides robustness to misspecification of either the treatment-assignment model or the outcome-regression model, although it does not protect against residual or unmeasured confounding [19]. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were estimated from the weighted regression models.

Marginal response probabilities were subsequently estimated by standardizing model-based predictions over the weighted overlap population. Absolute risk differences (RDs) between treatment strategies were derived from these marginal probabilities and are reported in percentage points with 95% CIs [26].

An overall test of association between initial treatment strategy and each outcome was performed from the weighted outcome model. Pairwise comparisons between treatment strategies were subsequently evaluated, with Holm adjustment applied to pairwise p values within each outcome to account for multiple comparisons.

Two-sided p values <0.05 were considered statistically significant. Given the observational design and modest sample size, effect estimates, confidence intervals, and consistency across analyses were considered alongside p values when interpreting the findings.

Sensitivity analyses

Sensitivity analyses were performed to examine the robustness of the primary ≥50% response findings.

First, unweighted multivariable logistic regression models were performed using the same six prespecified covariates.

Second, Firth penalized logistic regression was performed to reduce small-sample bias and improve estimation stability under sparse outcome distributions.

The ≥75% response analysis was treated as a prespecified secondary effectiveness analysis rather than a sensitivity analysis.

Exploratory subgroup analyses

Exploratory subgroup analyses were performed to evaluate potential heterogeneity according to : migraine phenotype (episodic migraine versus chronic migraine); and vestibular migraine status (with versus without vestibular migraine). Treatment-by-subgroup interaction terms were assessed when estimable.

Because several subgroup strata contained small numbers of patients and events, subgroup estimates were interpreted cautiously. Where sparse outcome distributions resulted in complete or near-complete separation or otherwise rendered model estimates unstable, the corresponding treatment effect was reported as not estimable, and no inferential conclusion regarding effect modification was drawn from that stratum.

Subgroup analyses were considered hypothesis-generating.

Statistical software

All statistical analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria). Two-sided p values < 0.05 were considered statistically significant.

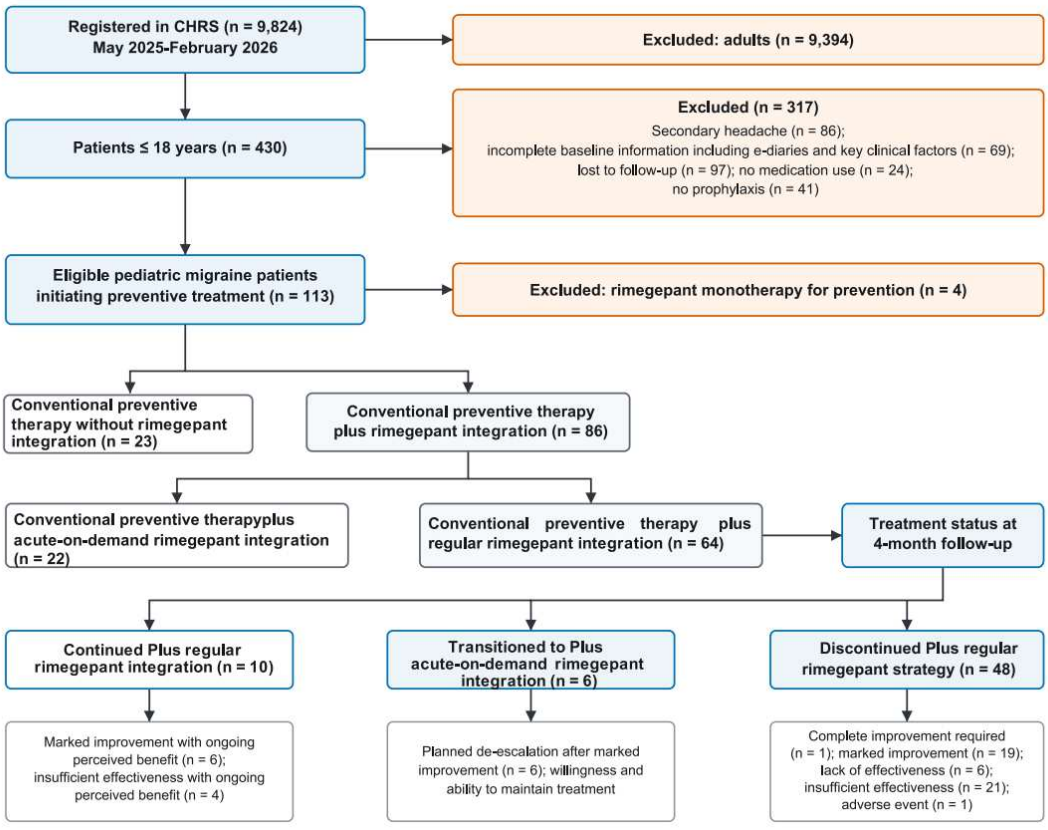
Results

Patient characteristics and initial treatment strategies

Among 9,824 individuals registered in the CHRS, 109 patients aged ≤18 years with migraine met the prespecified eligibility criteria were included in the analytic cohort (Figure 1). According to the initial preventive treatment strategy, 23 patients received conventional preventive therapy without rimegepant integration, 64 received conventional preventive therapy plus regular rimegepant integration, and 22 received conventional preventive therapy plus rimegepant acute-on-demand integration.

Among the 64 patients initially receiving regular rimegepant integration, treatment trajectories during the 4-month follow-up were heterogeneous. Ten patients continued regular rimegepant , six transitioned to an acute-on-demand strategy, and 48 discontinued regular rimegepant integration. Reasons for treatment modification included clinical improvement with perceived benefit, insufficient effectiveness, lack of effectiveness, and adverse events (Figure 1; Table 3).

Figure 1. Study flow and treatment trajectories according to the initial preventive treatment strategy.



Abbreviation: CHRS, China Headache and Vertigo Registry System.

Baseline clinical characteristics according to treatment strategy are summarized in Table 1. The cohort included 61 females and 48 males; 33 patients had chronic migraine and 76 had episodic migraine. Mean baseline MHDs were 13.4 ± 10.7 days/month, with a median of 10 days/month (interquartile range, 4–22 days/month). The median headache duration was approximately 2.9 years. Forty-five patients (41.3%) were aged ≥ 15 years. Fifty patients received one preventive medication, and 59 received at least two preventive medications. Vestibular migraine was present in 43 patients (39.4%).

The treatment groups differed descriptively in several baseline clinical characteristics, including MHDs, migraine phenotype, headache duration, and previous treatment characteristics (Table 1), supporting the prespecified need for confounding adjustment.

Table 1. Baseline clinical characteristics according to initial treatment strategy

Variable	Conventional preventive therapy without rimegepant integration (n=23)	conventional preventive therapy plus regular rimegepant integration (n=64)	Conventional preventive therapy plus acute-on-demand rimegepant integration (n=22)	Maximum absolute SMD
Age, years, mean (SD)	14.74 (2.12)	14.69 (2.27)	14.59 (2.34)	0.044
Male sex, n (%)	7 (30.4)	31 (48.4)	10 (45.5)	0.249
Migraine characteristics				
Monthly headache days, mean (SD)	12.09 (11.15)	15.37 (11.62)	6.05 (6.33)	0.650

Migraine duration, years, mean (SD)	1.94 (2.11)	3.02 (2.23)	3.55 (2.55)	0.469
Chronic migraine, n (%)	4 (17.4)	28 (43.8)	1 (4.5)	0.683
Migraine with aura, n (%)	5 (21.7)	8 (12.5)	2 (9.1)	0.238
Patient burden				
MIDAS score,median (IQR)	51.60 (65.26)	65.69 (91.69)	27.29 (33.69)	0.400
HIT-6 score, mean (SD)	46.91 (27.47)	53.03 (21.20)	56.55 (21.04)	0.270
GAD-7 score, mean (SD)	5.00 (4.13)	6.42 (5.85)	7.00 (4.93)	0.276
PHQ-9 score, mean (SD)	6.17 (4.12)	7.67 (6.83)	8.09 (7.03)	0.220
PSQI score, mean (SD)	6.15 (3.50)	7.21 (3.73)	6.06 (2.80)	0.224
Vestibular features				
Vestibular migraine, n (%)	11 (47.8)	26 (40.6)	6 (27.3)	0.288
Motion sickness, n (%)	12 (52.2)	25 (39.1)	13 (59.1)	0.271
Family history of headache, n (%)	7 (30.4)	31 (48.4)	14 (63.6)	0.463
Prior treatment				
Previous analgesics, n (%)	4 (17.4)	22 (34.4)	10 (45.5)	0.419
Previous preventive treatment, n (%)	4 (17.4)	17 (26.6)	3 (13.6)	0.218
Baseline preventive polytherapy, n (%	13 (56.5)	37 (57.8)	9 (40.9)	0.228

Note: Data are presented as mean (SD), median (IQR), or n (%) as appropriate. Standardized mean differences (SMDs) provide a standardized assessment of covariate imbalance independent of sample size; an absolute SMD <0.1 was considered indicative of adequate balance. Missing values were observed for MIDAS (n=7), PSQI (n=18), and HIT-6 (n=14).

Abbreviations: SD, standard deviation; IQR, interquartile range; SMD, standardized mean difference; GAD-7, Generalized Anxiety Disorder-7; HIT-6, Headache Impact Test-6; IQR, interquartile range; MIDAS, Migraine Disability Assessment Scale; PHQ-9, Patient Health Questionnaire-9; PSQI, Pittsburgh Sleep Quality Index.

Covariate balance after CBPS-based overlap weighting

After CBPS-based overlap weighting, all six prespecified baseline covariates achieved excellent balance across treatment strategies (Supplementary Table S1). The maximum SMD after weighting was < 0.001 for age category, baseline MHDs, headache duration, migraine phenotype, and baseline preventive medication burden (Supplementary Table S1).

The effective sample sizes after weighting were 16.49 for conventional preventive therapy alone, 40.21 for plus regular rimegepant integration, and 13.83 for plus acute-on-demand rimegepant integration, with an overall effective sample size of 57.04 (Supplementary Table S1). These diagnostics indicated substantial improvement in measured baseline comparability, while also reflecting the reduced information available in the smaller treatment groups after weighting.

Association between initial preventive treatment strategies and 4-month treatment response

Adjusted analyses using CBPS-based overlap weighting and doubly robust regression are presented in Table 2 and Figure 2.

For the primary outcome of ≥ 50% reduction in MHDs at 4 months, adjusted response probabilities were 51.2% (95% CI, 30.1–72.3%) with conventional preventive therapy alone, 67.5% (95% CI, 53.6–81.4%) with plus regular rimegepant integration, and 78.6% (95% CI, 62.5–94.7%) with plsu acute-on-demand rimegepant integration. The overall association between initial treatment strategy and primary outcome was not statistically significant (overall p = 0.196) (Table 2, Figure 2A).

Compared with conventional preventive therapy alone, plus regular rimegepant integration was associated with a numerically higher probability of ≥ 50% response (adjusted OR, 2.20; 95% CI, 0.65–7.50, Holm-adjusted p = 0.207), corresponding to 16.3 percentage points (95% CI, −8.8 to 41.4). Plus acute-on-demand rimegepant

integration showed a similarly favorable numerical pattern (adjusted OR, 4.19; 95% CI, 0.87–20.16; Holm-adjusted p = 0.074), with an adjusted risk difference of 27.4 percentage points (95% CI, −1.4 to 56.2) (Table 2, Figure 2A). Thus, although both rimegepant-containing strategies showed higher point estimates, the primary pairwise comparisons remained statistically uncertain.

For the secondary outcome of ≥75% reduction in MHDs, adjusted response probabilities were 37.2% (95% CI, 20.0–54.4%), 60.4% (95% CI, 47.1–73.7%), and 76.6% (95% CI, 60.3–92.8%) for conventional preventive therapy alone, plus regular rimegepant integration, and plus acute-on-demand rimegepant integration, respectively. The overall association was statistically significant (overall p = 0.035).

Compared with conventional preventive therapy alone, plus regular rimegepant integration was associated with higher odds of ≥75% response (adjusted OR, 3.32; 95% CI, 1.03–10.74; Holm-adjusted p = 0.045), corresponding to an adjusted risk difference of 23.2 percentage points (95% CI, 2.0–44.4). Plus acute-on-demand integration was also associated with higher odds of ≥75% response (adjusted OR, 8.47; 95% CI, 1.62–44.20; Holm-adjusted p = 0.011), with an adjusted risk difference of 39.4 percentage points (95% CI, 12.7–66.1). Because ≥75% response was a secondary outcome and confidence intervals were wide, these findings were interpreted as supportive and hypothesis-generating (Table 2, Figure 2B).

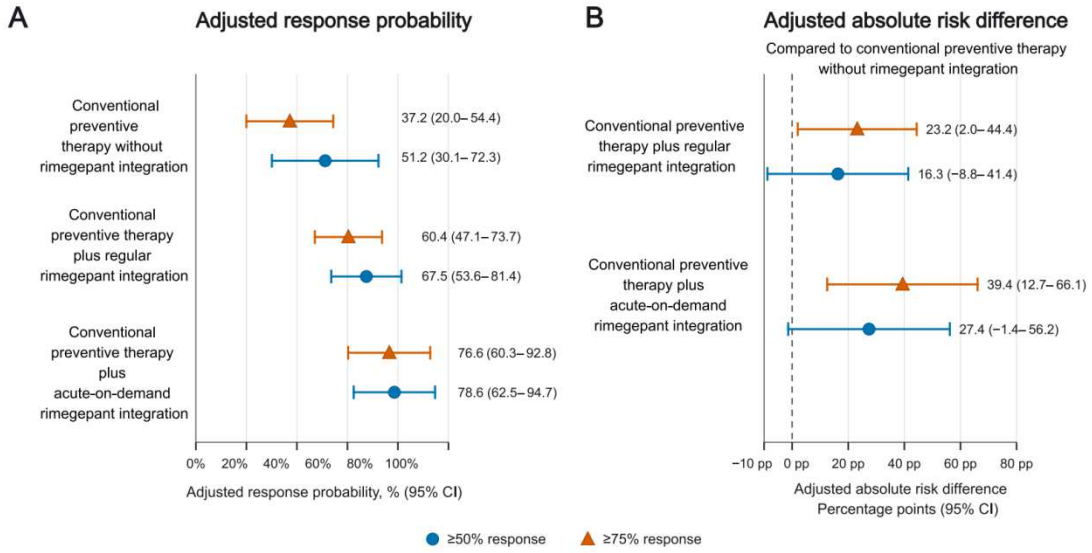
Table 2. Adjusted 4-month treatment response according to initial preventive treatment strategy

Outcome	Initial preventive treatment strategy	Observed response, n/N (%)	Adjusted OR (95% CI)	Holm-adjusted pairwise P value	Adjusted response probability, % (95% CI)	Adjusted risk difference, percentage points (95% CI)	Overall *P* value
≥50% reduction in MHDs	Conventional preventive therapy without rimegepant integration	11/23 (47.8)	Reference	—	51.2 (30.1–72.3)	Reference	0.196
	conventional preventive therapy plus regular rimegepant integration	43/64 (67.2)	2.20 (0.65–7.50)	0.207	67.5 (53.6–81.4)	16.3 (−8.8 to 41.4)	
	Conventional preventive therapy plus acute-on-demand rimegepant integration	17/22 (77.3)	4.19 (0.87–20.16)	0.074	78.6 (62.5–94.7)	27.4 (−1.4 to 56.2)	
≥75% reduction in MHDs	Conventional preventive therapy without rimegepant integration	8/23 (34.8)	Reference	—	37.2 (20.0–54.4)	Reference	0.035
	Conventional preventive therapy plus regular rimegepant integration	36/64 (56.3)	3.32(1.03–10.74)	0.045	60.4 (47.1–73.7)	23.2 (2.0 to 44.4)	
	Conventional preventive therapy plus acute-on-demand rimegepant integration	16/22 (72.7)	8.47 (1.62–44.20)	0.011	76.6 (60.3–92.8)	39.4 (12.7 to 66.1)	

412 Note: Adjusted estimates were obtained using covariate-balancing propensity score–based overlap weighting and doubly robust logistic regression
413 adjustment. Pairwise p values were adjusted separately plusin each outcome using the Holm method; overall p values represent global tests of
414 association between initial treatment strategy and outcome.

Abbreviations: ATO, average treatment effect in the overlap population; CBPS, covariate-balancing propensity score; CI, confidence interval; MHDs, monthly headache days; OR, odds ratio.

Figure 2. Adjusted response probabilities and risk differences for treatment outcomes according to initial preventive strategy



Sensitivity analyses

Sensitivity analyses were performed to assess the robustness of the treatment-association patterns (Supplementary Table S2). Firth penalized logistic regression produced estimates that were directionally consistent plus the primary CBPS-based overlap-weighted doubly robust analyses. The ≥75% response remained a prespecified secondary effectiveness outcome; its presentation in Supplementary Table S2 was used to assess consistency across modeling approaches rather than to redefine the outcome hierarchy.

Treatment trajectories following initiation of regular rimegepant

Among the 64 patients initially assigned to regular rimegepant integration, treatment trajectories during the 4-month follow-up were heterogeneous (Figure 1; Table 3).

Ten patients (15.6%) continued regular rimegepant integration. Six continued after marked clinical improvement plus ongoing perceived benefit, whereas four continued despite incomplete effectiveness because some ongoing benefit was perceived.

Six patients (9.4%) transitioned from regular integration to acute-on-demand rimegepant integration. All six transitions occurred following marked clinical improvement and represented planned treatment de-escalation while retaining rimegepant as an acute treatment option.

Forty-eight patients (75.0%) discontinued regular rimegepant integration during follow-up. Reasons included complete improvement requiring no further preventive treatment (n = 1), marked improvement (n = 19), insufficient effectiveness (n = 21), lack of effectiveness (n = 6), and an adverse event (n = 1). Accordingly, discontinuation reflected heterogeneous clinical circumstances and should not be interpreted uniformly as treatment failure.

Table 3. Treatment trajectories and reasons for treatment modification among patients initially receiving regular rimegepant integration (n = 64)

A. Treatment trajectory at 4-month follow-up

Treatment trajectory	n (%)	Mean treatment duration, months
Continued regular rimegepant integration	10 (15.6)	3.33
Transitioned to acute-on-demand rimegepant integration	6 (9.4)	3.23

Treatment trajectory	n (%)	Mean treatment duration, months
Discontinued regular rimegepant integration	48 (75.0)	2.94

B. Reasons according to final treatment trajectory

Final treatment trajectory	Reason	n
Continued regular rimegepant integration	Marked improvement plus ongoing perceived benefit	6
	Insufficient effectiveness but ongoing perceived benefit	4
Transitioned to acute-on-demand rimegepant integration	Planned de-escalation after marked improvement	6
Discontinued regular rimegepant integration	Complete improvement requiring no further preventive treatment	1
	Marked improvement	19
	Insufficient effectiveness	21
	Lack of effectiveness	6
	Adverse event (nausea)	1

Note: Percentages are calculated among the 64 patients who initially received regular rimegepant integration. Abbreviation: n, number of patients.

Documented adverse events

Few adverse events were documented during follow-up. One patient receiving rimegepant experienced nausea that resulted in treatment discontinuation. No serious adverse events were documented. Given the descriptive ascertainment of adverse events through routine clinical records and the limited sample size and follow-up

duration, these findings were not used to estimate the incidence of adverse events or establish treatment safety.

Exploratory subgroup analyses

Exploratory subgroup analyses evaluated treatment-response patterns according to migraine phenotype and vestibular migraine status (Supplementary Table S4).

For migraine phenotype, estimates among patients plus chronic migraine were limited by small subgroup sizes and sparse outcome distributions. In particular, the response estimate for the acute-on-demand rimegepant strategy among patients with chronic migraine was not estimable because of sparse outcome data. Consequently, a reliable treatment-by-migraine-phenotype interaction could not be established, and no conclusion regarding effect modification by migraine phenotype was drawn.

For vestibular migraine status, adjusted treatment-response patterns were generally similar among patients with and without vestibular migraine, and there was no evidence of treatment-effect modification (treatment × vestibular migraine interaction, Wald $p = 0.493$). These subgroup findings should be considered exploratory.

Discussion

In this multicenter real-world cohort of children and adolescents with migraine, we evaluated three initial strategies for integrating rimegepant into preventive management: conventional preventive therapy without rimegepant integration, conventional preventive therapy plus regular rimegepant integration, and conventional preventive therapy plus acute-on-demand rimegepant integration. After CBPS-based overlap weighting and doubly robust adjustment for measured baseline differences, both rimegepant-containing strategies showed numerically higher adjusted probabilities of achieving the primary outcome of ≥50% reduction in MHDs than

conventional preventive therapy without rimegepant integration. However, the overall association and pairwise comparisons for the primary outcome did not reach statistical significance, and confidence intervals remained wide. More pronounced associations were observed for the secondary ≥75% response outcome. Patients initially receiving regular rimegepant also showed heterogeneous subsequent treatment trajectories. Taken together, these findings provide preliminary real-world evidence regarding how an oral CGRP receptor antagonist may be incorporated into preventive management in younger patients, while the observational design and modest sample size require cautious interpretation.

The present findings should be considered within the rapidly evolving evidence base for CGRP-targeted treatment in pediatric migraine. Randomized evidence now supports fremanezumab for episodic migraine in children and adolescents [9], while earlier real-world studies described CGRP monoclonal antibody use in adolescent and young-adult populations [10,11]. More directly relevant to the present study, Shin et al. reported a multicenter retrospective study of gepants used for headache prevention in children and adolescents, including rimegepant [12]. Tourlas et al. subsequently described acute rimegepant use in adolescents [13], and Lim et al. provided pediatric pharmacokinetic and tolerability data following a single weight-adjusted dose [14]. These studies substantially extend the pediatric evidence base but primarily address individual CGRP-targeted treatments rather than alternative ways of integrating rimegepant into an existing preventive regimen.

The PRIME-Teen study provides an especially relevant comparator. In an exploratory analysis of the German Pain e-Registry, 422 adolescents with high-burden migraine contributed treatment episodes involving conventional oral preventives and CGRP monoclonal antibodies. CGRP monoclonal antibody episodes were associated with substantially greater 6-month treatment persistence and a higher proportion of patients achieving a ≥50% reduction in MHDs than earlier conventional preventive episodes. Importantly, PRIME-Teen used a retrospective, non-randomized, sequential

515 treatment-episode design, and its findings were explicitly characterized as hypothesis-
516 generating rather than evidence of comparative effectiveness [15].

517 Our study complements PRIME-Teen but addresses a different clinical question.
518 PRIME-Teen compared different preventive treatment episodes, with CGRP
519 monoclonal antibodies generally occurring after earlier conventional preventive
520 treatment, whereas our study classified patients according to alternative initial
521 strategies within a concurrent preventive-management framework. All patients in our
522 cohort were candidates for preventive treatment and received conventional preventive
523 therapy as the background approach; rimegepant was either not incorporated, added
524 on a regular preventive schedule, or incorporated as an acute-on-demand component
525 of the overall strategy. Moreover, unlike a monoclonal antibody used specifically for
526 prevention, rimegepant has both acute and preventive therapeutic applications in
527 adults. This dual-use characteristic creates clinically distinct patterns of integration
528 and subsequent treatment modification that are not captured by a simple CGRP-
529 targeted-versus-conventional treatment comparison. In Chinese adults, prospective
530 multicenter real-world data have likewise described rimegepant use in both acute and
531 preventive settings [16], but pediatric strategy integration has not been specifically
532 evaluated.

533 The primary ≥50% response findings warrant particular caution. Adjusted response
534 probabilities were 51.2% with conventional preventive therapy, 67.5% with regular
535 rimegepant integration, and 78.6% with acute-on-demand rimegepant integration.
536 Nevertheless, the corresponding adjusted risk differences versus conventional
537 preventive therapy—16.3 percentage points for regular integration and 27.4
538 percentage points for acute-on-demand integration—had confidence intervals that
539 included the null. Thus, the direction and magnitude of the point estimates may be
540 clinically informative, but the present data do not establish superiority of either
541 rimegepant-containing strategy. This uncertainty is consistent with the modest cohort

size and reduced effective sample sizes after overlap weighting, particularly in the conventional and acute-on-demand groups.

By contrast, stronger associations were observed for the prespecified secondary ≥75% response outcome. Both regular and acute-on-demand rimegepant integration were associated with higher adjusted probabilities of ≥75% response than conventional preventive therapy alone, with adjusted risk differences of 23.2 and 39.4 percentage points, respectively. Although these findings raise the possibility that rimegepant-containing strategies may be associated with a greater depth of clinical improvement in some patients, they should not be interpreted as confirmatory evidence. The ≥75% endpoint was secondary, confidence intervals remained relatively wide, and residual or unmeasured confounding remains possible despite excellent balance for the six prespecified measured covariates. These findings are therefore best regarded as hypothesis-generating.

An interesting finding was the favorable response pattern observed with the acute-on-demand rimegepant integration strategy. In this group, rimegepant was used for acute migraine attacks while conventional preventive therapy was maintained as the background treatment. The adjusted probability of achieving the primary ≥50% response was numerically higher than with conventional preventive therapy without rimegepant integration, although the confidence interval for the risk difference included the null. A stronger association was observed for the secondary ≥75% response outcome. These findings should therefore be interpreted as an association with the overall initial treatment strategy rather than as evidence that intermittent rimegepant administration itself provides a preventive effect.

The dual acute and preventive applications of rimegepant provide relevant context for this treatment pattern. In adults, rimegepant has demonstrated efficacy both for the acute treatment of individual migraine attacks and when administered on a regular preventive schedule [27, 28]. Importantly, real-world and longitudinal studies suggest that repeated acute-on-demand use may provide clinically meaningful responses

across attacks and may also be accompanied by improvement in overall migraine burden over time [29-31]. In a 52-week Chinese study, long-term as-needed rimegepant treatment remained effective for acute migraine management and was associated with improvement in migraine-related outcomes during follow-up [32]. These observations provide clinical context for the favorable outcomes observed in our acute-on-demand group, although they should not be interpreted as evidence that as-needed rimegepant is equivalent to scheduled preventive treatment.

Several alternative explanations should also be considered. Selection of the acute-on-demand strategy was non-randomized and may have reflected headache burden, migraine phenotype, previous treatment experience, clinician judgment, and patient or guardian preferences. Although overlap weighting achieved excellent balance across the six prespecified measured baseline covariates, residual and unmeasured confounding cannot be excluded. In addition, all patients in the acute-on-demand group continued conventional preventive therapy; therefore, the observed 4-month reduction in headache frequency cannot be attributed specifically to rimegepant. Nevertheless, the findings raise a clinically relevant hypothesis regarding flexible treatment integration that warrants prospective evaluation.

The heterogeneous treatment trajectories observed after initiation of regular rimegepant provide a complementary perspective on flexible treatment integration in routine practice. Among the 64 patients initially receiving regular rimegepant integration, 10 continued regular treatment, 6 transitioned to acute-on-demand integration, and 48 discontinued regular integration during follow-up. Importantly, these trajectories reflected heterogeneous clinical circumstances. All six transitions to acute-on-demand use were documented following marked clinical improvement, while discontinuation occurred after complete or marked improvement in some patients and because of insufficient or absent effectiveness in others. Thus, discontinuation of regular rimegepant should not be interpreted uniformly as treatment failure.

PRIME-Teen primarily compared CGRP-targeted monoclonal antibodies with conventional oral preventive therapies, whereas our study evaluated different strategies for integrating an oral CGRP receptor antagonist into preventive management. This distinction is particularly relevant when our findings are considered alongside PRIME-Teen, in which treatment persistence represented an important real-world outcome for preventive CGRP monoclonal antibody therapy [15]. For an oral agent such as rimegepant, which can be incorporated into treatment in both regular and acute-on-demand patterns, persistence with regular dosing may not fully capture the clinical course. Transition from regular to acute-on-demand use after improvement may instead represent treatment de-escalation within an individualized management strategy. Accordingly, we considered these post-initiation changes as treatment trajectories rather than comparative persistence outcomes. Future prospective studies should distinguish discontinuation due to insufficient effectiveness or tolerability from treatment reduction following clinical improvement.

Safety considerations

Few adverse events were documented during the 4-month follow-up. One patient discontinued rimegepant because of nausea, and no serious adverse events were documented. Although these observations are broadly consistent with the tolerability profile reported in previous rimegepant studies [12-14, 33], they should not be interpreted as establishing safety in children and adolescents. The present study was not designed or powered for safety evaluation, adverse-event ascertainment relied on routine clinical documentation rather than systematic prospective surveillance, and the relatively short follow-up may have limited detection of uncommon or delayed events. Larger prospective studies with standardized adverse-event monitoring and longer follow-up are needed.

Exploratory subgroup findings

Exploratory subgroup analyses did not provide robust evidence of treatment-effect heterogeneity according to migraine phenotype or vestibular migraine status. For migraine phenotype, interpretation was substantially limited by small subgroup sizes and sparse outcome distributions; in particular, the treatment effect for the acute-on-demand strategy among patients with chronic migraine was not estimable. Accordingly, no reliable conclusion regarding effect modification by migraine phenotype can be drawn. For vestibular migraine status, treatment-response patterns were generally similar between patients with and without vestibular migraine, and the treatment-by-vestibular migraine interaction was not statistically significant (Wald p=0.493). These findings should not be interpreted as evidence that treatment effects are equivalent across subgroups, but rather as indicating that the current study provides insufficient evidence to establish clinically meaningful treatment-effect heterogeneity.

Strengths and limitations

This study has several strengths. First, it addresses a clinically relevant question that differs from previous pediatric studies evaluating individual CGRP-targeted therapies: how an oral CGRP receptor antagonist may be integrated into an existing preventive-treatment framework using alternative initial treatment strategies. Second, the multicenter registry-based design reflects treatment patterns and clinical decision-making in routine practice. Third, treatment exposure was defined according to the initial treatment strategy rather than reclassified according to subsequent treatment modification, allowing post-initiation changes to be evaluated separately as treatment trajectories. Fourth, CBPS-based overlap weighting achieved excellent balance across the six prespecified measured baseline covariates, and doubly robust outcome regression provided additional protection against model misspecification. Finally, evaluation of both conventional ≥50% response and the more stringent ≥75% response, together with treatment trajectories, provides complementary perspectives on short-term clinical outcomes.

Several limitations should be acknowledged. First, this was an observational study, and treatment allocation was determined in routine clinical practice rather than randomized. Although CBPS-based overlap weighting achieved excellent balance across the six prespecified measured baseline covariates, residual and unmeasured confounding remains possible; therefore, the observed associations should not be interpreted causally. Second, the overall sample size was modest, and the conventional preventive and acute-on-demand groups were relatively small. Weighting further reduced the effective sample size, resulting in limited precision and wide confidence intervals for several estimates. Third, treatment selection may have been influenced by clinical characteristics, clinician judgment, patient or family preferences, treatment accessibility, or other factors not fully captured in the registry. Fourth, follow-up was limited to 4 months, precluding assessment of longer-term effectiveness, durability of response, treatment adaptation, and safety. Fifth, detailed post-initiation treatment trajectories were available primarily for patients initially receiving regular rimegepant integration and therefore could not be compared formally across all three strategies. Sixth, adverse events were identified from routine clinical documentation rather than systematic prospective surveillance. Finally, exploratory subgroup analyses were constrained by small numbers and sparse outcome distributions in some strata, and some treatment effects were not estimable.

Conclusion

In conclusion, to our knowledge, this is the first multicenter real-world study conducted in China to compare alternative initial strategies for integrating rimegepant into preventive migraine management in children and adolescents. Both rimegepant-containing strategies showed numerically higher adjusted probabilities of achieving the primary ≥50% reduction in MHDs than conventional preventive therapy alone, although the primary comparisons remained statistically uncertain. More pronounced associations were observed for the secondary ≥75% response outcome. The heterogeneous treatment trajectories following regular rimegepant initiation further

suggest that continuation, transition to acute-on-demand use, and discontinuation may represent distinct clinical adaptations rather than uniform indicators of treatment success or failure. These findings should be regarded as preliminary and hypothesis-generating rather than evidence of treatment superiority. Larger prospective studies are needed to determine which patients may benefit from different approaches to integrating oral CGRP receptor antagonists into pediatric migraine management and to establish their longer-term effectiveness and safety.

List of abbreviations

CHRS, China Headache and Vertigo Registry Study

CI, confidence interval

HIT-6, Headache Impact Test-6

ICHD-3, International Classification of Headache Disorders, third edition

IHS, International Headache Society

MIDAS, Migraine Disability Assessment Scale

MHDs, monthly headache days

OR, Odds Ratio

SD, Standard Deviation

SMD, Standard Mean Difference

CBPS, Covariate-Balancing Propensity Score

OW, Overlap Weighting

ATO, average treatment effect in the overlap population

CGRP, Calcitonin Gene-Related Peptide

GAD-7, Anxiety Disorder Scale-7

PHQ-9, Patient Health Questionnaire-9

PSQI, Pittsburgh Sleep Quality Index

Declarations

Ethics approval and consent to participate

This study was constructed using data from the China Headache and Vertigo Registry System (CHRS), which was registered with ClinicalTrials.gov (NCT04939922; first

posted on June 14, 2021). The CHRS study was in accordance with the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of The Second Affiliated Hospital of Zhejiang University School of Medicine. Written informed consent was obtained from all participants and/or their legal guardians at enrollment in the registry.

Consent for publication

All authors authorize the publication.

Availability of data and materials

The data presented in this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors contributed to the conception and design of the study. ZXZ and JXF contributed equally to this work and wrote the original draft. JYS, MTZ, LLG, YHX, MNY, JHH, FFL, HXP and XDY collected and curated the clinical data. ZXZ and JXF performed the statistical analyses. KML reviewed and revised the final manuscript. KML also supervised the study. All authors approved the final version submitted for publication.

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