Early clinical experience with a monoclonal antibody against the calcitonin gene-related peptide receptor in adolescents with migraine: A case series

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Abstract
Management of migraine in adolescents poses a great challenge, as many of the approved pharmacological migraine preventive agents have age restrictions. Following favorable safety and efficacy reports of the new class agent calcitonin gene-related peptide (CGRP) monoclonal antibody for use in migraine prevention, there is growing interest in its application in pediatric migraine. We present here a case series detailing our experience of using erenumab, a CGRP monoclonal antibody, in six adolescent patients. Two patients had a reduction of at least 50% in the mean number of monthly migraine days, one patient reported subjective improvement, while three patients did not respond to the first dose of erenumab and discontinued treatment. One patient reported constipation associated with erenumab use. We speculate that CGRP monoclonal antibody could potentially be a viable option in adolescent patients with migraine. Further evidences that support efficacy and safety of erenumab in this group is needed.

Keywords
Calcitonin gene-related peptide, erenumab, paediatric, headache, preventive

Introduction
Migraine is a neurological condition with a high cumulative lifetime risk, and is one of the top few medical conditions associated with years lived with disability (YLD). Despite its high prevalence and morbidity, preventive treatment options have limited efficacy and are associated with a range of side effects that can result in poor adherence to therapy. Management of migraine in adolescents presents an even greater challenge due to a paucity of data to guide the choice of effective agents in this population. The majority of randomised controlled studies on the agents used in adults fail to demonstrate superiority to placebo in pediatric patients with migraine. Off-label prescribing for the treatment of migraine in children and adolescents, as well as undertreatment, are common, as many of the approved pharmacological agents have age restrictions.

More recent research has led to the development of monoclonal antibodies targeting either the CGRP molecule or receptor, opening up new vistas in migraine-specific treatment. Erenumab is a human monoclonal antibody against the calcitonin gene-related peptide (CGRP) receptor and is the first of this drug class to obtain US Food and Drug Administration (FDA) approval for use in migraine prevention. The pivotal clinical trials on which its approval were based involved subjects aged 18–65 years. Following favourable safety and efficacy reports of erenumab use in adults, there is a growing interest of its application in pediatric migraine. There is an ongoing clinical trial evaluating the safety and efficacy of erenumab in migraine prevention in children (i.e. those 6–<12 years old) and adolescents (i.e. those 12–<18 years) with chronic migraine. Recommendations have been provided by the members of the paediatric and adolescent headache special interest group of the American Headache Society on the clinical use of CGRP monoclonal...
antibodies in children and adolescents. We present here a case series detailing the responses of adolescent patients in the age range 15–18 years to erenumab, highlighting a few cases and providing a summary of the six patients’ demographics and responses (Table 1).

**Case 1**

A 15-year-old Chinese girl with a past medical history of four years’ duration of migraine with visual aura was having migraines at least once per week, with each attack so debilitating that she had to miss school. This was of concern, as a major examination was imminent. During discussion with the patient and her parents on conventional oral preventive treatment, potential central nervous system side effects were raised as a major concern in view of the impending exam. The patient was screened for contraindications, and erenumab was offered as an off-label option. A detailed explanation on the expected side effects from adult studies and the lack of comprehensive clinical data specific to her age group were discussed. The patient and her parents opted for a trial of 70 mg erenumab. The patient and her parents were counselled on the lack of data in terms of efficacy, safety profile and dosing parameters on the usage of CGRP monoclonal antibody in her age group. After one month of treatment, her monthly migraine days (MMD) decreased from 10 days to 1 day. She had constipation for a week after starting treatment which spontaneously resolved thereafter. Her family opted to continue the medication after the first dose. She has yet to be reviewed on her subsequent clinical response at the time of writing.

**Case 2**

A 15-year-old Chinese boy with intermittent migraines had been treated sequentially with propranolol, atenolol, verapamil and flunarizine without effect over eight months of follow-up. His headaches were complicated by depression, anxiety and fibromyalgia. A single dose of 70 mg erenumab had no effect on his MMD (eight days a month), and the patient and family opted not to continue the medication. No side effects were reported.

**Case 3**

A 16-year-old Caucasian girl with a past medical history of fibromyalgia and chronic left shoulder pain diagnosed as chronic regional pain syndrome following an injury three years prior presented with daily migraines. She was taking analgesics at a frequency that would have predisposed her to medication overuse headache. Because of her reluctance to use more oral medication, 70 mg erenumab was offered. She responded well to erenumab (MMD=10 days), and opted to continue treatment for six months. The patient was monitored for response as well as pregnancy status.

**Discussion**

Our small case series consists of six adolescent patients with episodic or chronic migraine treated with a CGRP receptor monoclonal antibody. The first patient noted a period of constipation after the initiation of 70 mg erenumab, whereas no side effects were noted in the others. Constipation has been reported in a Phase III trial of erenumab in episodic migraine patients, but this did not reach a statistically significant difference between subjects on placebo or 70 or 140 mg doses. The overall favorable side-effect profile observed in our case series is in keeping with the original studies in adult populations.

Among the six adolescent patients treated, four had a history of prior treatment failure with three or more migraine oral preventives. This reflects the fact that there is a subgroup of adolescents as well as adults who can be difficult to treat with conventional migraine prophylactics. Amongst these four patients, two patients had no response, while one patient reported a subjective improvement of symptoms. The remaining patient had a reduction in mean MMD from 30 to 1 day. She had constipation for a week after starting treatment which spontaneously resolved thereafter. Her family opted to continue the medication after the first dose. She has yet to be reviewed on her subsequent clinical response at the time of writing.

| No. | Age | Sex | Race | Type of migraine | Side effects | Medical history | Previous number of preventive treatments used | Initial monthly migraine days | Post-treatment monthly migraine days |
|-----|-----|-----|------|------------------|--------------|----------------|---------------------------------------------|-------------------------------|-----------------------------------|
| 1   | 15  | Female | Chinese | Episodic migraine | Constipation for one week | None | 0 | 10 | 1 |
| 2   | 15  | Male | Chinese | Episodic migraine | None | Depression and anxiety | 3 | 8 | 8 |
| 3   | 16  | Female | Caucasian | Chronic migraine | None | Fibromyalgia | 4 | 30 | 10 |
| 4   | 17  | Male | Caucasian | Chronic migraine | None | Fibromyalgia | 4 | 28 | 28 (subjectively better, opted to continue treatment) |
| 5   | 18  | Female | Caucasian | Chronic migraine | None | Depression and anxiety | 5 | 28 | 28 |
| 6   | 18  | Female | Eurasian | Chronic migraine | None | None | 1 | 30 | 30 |
treatment has several advantages. Its specificity in the trigeminal pain system reduces unwanted off-target side effects. By blocking the CGRP ligand and lowering the migraine frequency, this may also interrupt the processes involved in chronification, which is associated with significant disability. In addition, erenumab has a long half-life that allows for monthly administration. This may be advantageous in the paediatric population which has been reported to have adherence issues.

Three of our patients did not respond after the first dose of erenumab, with no change in MMD. One other individual had a partial but clinically useful response. Experience in the pivotal studies indicates that a proportion of patients respond only when treatment is continued beyond a month. We were not able to assess whether this might be the case for our non-responding patients, as treatment was not continued after the initial dose. However, two patients responded with a decrease in MMD after treatment with monthly dosing of 70 mg erenumab. Plasma CGRP levels have been reported to be significantly elevated in children with migraine compared to non-migraine and non-headache controls. In the same study, those who required preventive treatment had significantly higher CGRP levels than those only on acute therapy. This supports the hypothesis that CGRP elevation may be similarly associated with migraine severity and chronicity in the younger population. Hence, the use of agents that modulates the CGRP pathway may potentially be beneficial.

Conclusion

Our small case series reported favorable response and tolerability to erenumab in two out of six adolescent patients, heterogeneous in terms of sex, race, and migraine type. This small sample highlighted real-world clinical experience of children and adolescents who can present with difficult-to-treat migraine early in life. Effective and well-tolerated migraine preventive therapies for children and adolescents are limited. Increasing the evidence base with good quality studies to provide age-appropriate guidance on the efficacy and safety of CGRP monoclonal antibody is urgently needed to fulfill the unmet needs in this population of migraine patients.

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Conflict of interest

H.K.H. has served in the Advisory Board and received honorarium from Novartis. Z.Y.J. and W.P. declare no conflict of interest.

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