Calcitonin gene related peptide monoclonal antibody treats headache in patients with active idiopathic intracranial hypertension

Andreas Yiangou  
University of Birmingham College of Medical and Dental Sciences  
https://orcid.org/0000-0001-8905-5734

James Mitchell  
University of Birmingham College of Medical and Dental Sciences

Vivek Vijay  
University of Birmingham College of Medical and Dental Sciences

Olivia Grech  
University of Birmingham College of Medical and Dental Sciences

Edward Bilton  
University of Birmingham College of Medical and Dental Sciences

Gareth Lavery  
University of Birmingham College of Medical and Dental Sciences

Claire Fisher  
University of Birmingham College of Medical and Dental Sciences

Julie Edwards  
University Hospitals Birmingham NHS Foundation Trust

Susan Mollan  
University Hospitals Birmingham NHS Foundation Trust

Alexandra Sinclair (✉ a.b.sinclair@bham.ac.uk)  
https://orcid.org/0000-0003-2777-5132

Case report

Keywords: CGRP monoclonal antibody, headache, idiopathic intracranial hypertension, papilloedema, raised intracranial pressure

DOI: https://doi.org/10.21203/rs.3.rs-40270/v1

License: ☒  This work is licensed under a Creative Commons Attribution 4.0 International License.  
Read Full License
Abstract

Background

The mechanisms driving headache in Idiopathic Intracranial Hypertension (IIH) are not fully understood. Headache is the dominant driver for disability and typically has migraine-like characteristics. There are currently no evidence-based therapeutics for headache in IIH, and consequently this is an important unmet need.

Case series

We report seven patients with confirmed IIH who initially presented with increased headache driven by raised intracranial pressure (ICP). The headaches had migraine-like characteristics which persisted despite resolution of papilloedema (ocular remission). These headaches responded markedly to Erenumab, a monoclonal antibody targeted against the calcitonin gene related peptide (CGRP) receptor. Importantly, there was a recurrence of raised ICP and papilloedema, however headaches did not recur whilst treated with Erenumab.

Conclusions

These cases suggest that CGRP could be a mechanistic driver for headache in patients with active IIH. Clinical trials evaluating safety and efficacy of CGRP monoclonal antibodies in active IIH would be of interest.

Introduction

Idiopathic intracranial hypertension (IIH) is a chronic debilitating disease characterised by raised intracranial pressure (ICP) that typically occurs in young, obese women. There is evidence of rapidly increasing incidence (350% increase in 10 years), in line with global obesity trends.(1, 2) Disability in IIH is predominantly driven by debilitating headaches.(3) Headaches in IIH most frequently have migraine-like characteristics.(4) Therapeutic strategies to prevent headache in IIH are an unmet need.(1, 4, 5)

We report seven patients with IIH whose presenting feature for raised ICP was headache. These headaches persisted despite resolution of papilloedema and had migraine-like characteristics. These headaches responded to Erenumab, a monoclonal antibody targeted against calcitonin gene related peptide (CGRP) receptor. However, of key interest, was that when raised ICP recurred with return of papilloedema, headaches did not recur but were blocked whilst they were treated with the CGRP monoclonal antibody.

Case Series

We describe 7 patients who presented with headaches in the setting of raised ICP and who met the diagnostic criteria for IIH. Their headaches persisted, even after resolution of papilledema, and had
migraine-like characteristics (photophobia, phonophobia, kinesophobia, nausea and throbbing pain) as is typical in IIH. (1, 4, 6) The mean (SD) duration of years since the IIH diagnosis was 2.4 (1.5). Their headaches persisted (> 15 days per month) and were resistant to conventional oral preventative treatments (failed > 3).(7)

These chronic migraine-like headaches were treated with a CGRP monoclonal antibody Erenumab (Aimovig®, Novartis) within the National Health Service (NHS) headache service at University Hospital Birmingham NHS Foundation Trust, UK as part of a free of charge scheme (Novartis). Detailed characteristics of the patients are documented in Table 1. The pathway for Erenumab delivery entailed a full headache and neuro-ophthalmology assessment at Erenumab initiation, including optical coherence tomography (OCT) imaging and dilated slit lamp fundus assessment, which confirmed complete resolution of papilloedema (Table 1). Patients were then commenced on Erenumab 70 mg four-weekly subcutaneous injections. In all cases the headache response (improvement in monthly headache days and/ or severity) was greater than 30% but less than 50% and hence, as per the local pathway, the dose was increased to 140 mg at 3 months. Patients were seen 3-monthly over a 12-month period. Follow-up visits involved headache diary evaluation of monthly moderate/severe headache days (MmsHD) (moderate to severe headaches lasting > 4 hours), all monthly headache days (MHD) (headaches of any severity lasting > 30 minutes), monthly analgesic frequency, headache severity, disability (Headache Impact Test – 6, HIT-6) and IIH symptoms (Table 1).
### Table 1
Patient characteristics

|                                | P1  | P2  | P3  | P4  | P5  | P6  | P7  | Mean (SD) |
|--------------------------------|-----|-----|-----|-----|-----|-----|-----|-----------|
| Age (years)                    | 42  | 34  | 46  | 24  | 36  | 25  | 25  | 33.1 (8.2) |
| Duration of IIH (years)        | 2   | 2   | 1   | 1   | 4   | 2   | 5   | 2.4 (1.5) |
| Headache exacerbation at IIH diagnosis | +++ | +++ | +++ | +++ | +++ | +++ | +++ |           |
| Duration of headaches from resolution of papilloedema to initiation of Erenumab (months) | 12  | 3   | 3   | 3   | 24  | 6   | 3   | 7.7 (7.9) |
| Preventative drug class failure \(^a\) | 4   | 3   | 3   | 4   | 5   | 4   | 3   | 3.7 (0.8) |
| Preventative drug class trial \(^b\) | 3   | 2   | 1   | 0   | 4   | 1   | 1   | 1.7 (1.4) |
| MmsHD 12 months prior          | 12  | 20  | 16  | 16  | 14  | 8   | 14  | 14.3 (3.5) | \(p = 0.778\) |
| MmsHD baseline                 | 13  | 17  | 15  | 20  | 14  | 11  | 12  | 14.6 (3.1) |           |
| MmsHD change at 3 months       | -3  | -6  | -9  | -9  | -2  | -6  | -4  | -5.6 (2.8) | \(p = 0.002\) |
| MmsHD change at relapse        | -5  | -13 | -6  | -13 | -7  | -10 | -6  | -8.6 (3.4) | \(p < 0.001\) |
| MHD 12 months prior            | 30  | 30  | 30  | 30  | 28  | 30  | 20  | 28.3 (3.7) | \(p = 0.593\) |
| MHD baseline                   | 30  | 30  | 27  | 30  | 30  | 30  | 25  | 28.9 (2.0) |           |
|                                | P1  | P2  | P3  | P4  | P5  | P6  | P7  | Mean (SD) |
|--------------------------------|-----|-----|-----|-----|-----|-----|-----|-----------|
| MHD change at 3 months         | -20 | 0   | -18 | -12 | -15 | -16 | -4  | -12.1 (7.4) |
|                                |     |     |     |     |     |     |     | p = 0.028 |
| MHD change at relapse          | -22 | 0   | 0   | -15 | -10 | -24 | -5  | -10.9 (9.9) |
|                                |     |     |     |     |     |     |     | p = 0.043 |
| Headache severity (NRS) baseline | 5.7 | 5.2 | 7.2 | 7.3 | 5.2 | 4.5 | 7.1 | 6.0 (1.2) |
| Headache severity (NRS) change at 3 months | 2   | -0.9 | 0.2 | -2.6 | 0.1 | 0.1 | -1.7 | -0.4 (1.5) |
|                                |     |     |     |     |     |     |     | p = 0.497 |
| Headache severity (NRS) change at relapse | 2.7 | -1.4 | -0.8 | -2.7 | -1.8 | -0.4 | -2.4 | -1.0 (1.8) |
|                                |     |     |     |     |     |     |     | p = 0.253 |
| Monthly analgesic days baseline | 2   | 6   | 6   | 20  | 7   | 4   | 12  | 8.1 (6.1) |
| Monthly analgesic days change at 3 months | 3   | -1   | -6 | -18  | 0   | -4  | -9  | -5.0 (7.0) |
|                                |     |     |     |     |     |     |     | p = 0.107 |
| Monthly analgesic days change at relapse | 0   | 0   | -5 | -18  | -7  | 1   | -10 | -5.6 (6.9) |
|                                |     |     |     |     |     |     |     | p = 0.075 |
| HIT-6 score baseline           | 68  | 65  | 70  | 75  | 66  | 68  | 63  | 67.9 (3.9) |
| HIT-6 score change at 3 months | -5  | -11 | -4  | -13 | 1   | -8  | 2   | -5.4 (5.7) |
|                                |     |     |     |     |     |     |     | p = 0.045 |
|                                | P1   | P2   | P3   | P4   | P5   | P6   | P7   | Mean (SD) |
|--------------------------------|------|------|------|------|------|------|------|-----------|
| HIT-6 score change at relapse  | -5   | -13  | -4   | -3   | 0    | -18  | -2   | -6.4 (6.6)| p = 0.041 |
| Frisén grade baseline (both eyes) | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0         |
| Frisén grade at relapse (worst eye) | 4    | 2    | 3    | 1    | 1    | 1    | 1    | 1.9 (1.2) |
| OCT global average RNFL thickness baseline worst eye (µm) | 118  | 93   | 123  | 113  | 107  | 118  | 103  | 110.7 (10.4)| p = 0.043 |
| OCT global average RNFL thickness at relapse worst eye (µm) | 326  | 140  | 174  | 132  | 116  | 151  | 202  | 177.3 (71.4)| p = 0.043 |
| BMI baseline                   | 31   | 46.2 | 35.2 | 37.3 | 42.1 | 29.4 | 28.8 | 35.7 (6.6)| p = 0.025 |
| BMI at relapse                 | 31.3 | 48.5 | 38.7 | 38   | 44.6 | 36.7 | 30.5 | 38.3 (6.5)| p = 0.025 |
| BMI change                     | 0.3  | 2.3  | 3.5  | 0.7  | 2.5  | 7.3  | 1.7  | 2.6 (2.3) |
| IIH characteristics baseline   | B, T | B, T | B, T | B, D, T | B, D, T | D, T | B, T |
| IIH characteristics at relapse | B, T, V | B, T, V | B, T, V | B, D, T | B, D, T | B, D, T | B, T |
| Side effects                   | CO   | HT, I | I   | CO, MC |
| Acetazolamide at baseline      | no   | no   | no   | no   | no   | no   | 500 mg | no |

Baseline indicates when Erenumab initiated. * p values indicate changes from baseline

a Failure defined as any: inadequate efficacy with appropriate dosing and treatment duration; intolerable adverse effects; contraindications preventing use.

b Trial defined as any of: inadequate efficacy with appropriate dosing and treatment duration; intolerable adverse effects

c Heidelberg Engineering SPECTRALIS, Heidelberg, Germany
At 6 months since commencing Erenumab

+++ severe

Abbreviations: P, Patient; IIH, Idiopathic intracranial hypertension; MmsHD, monthly moderate/severe days; MHD, all monthly headache days; NRS, Numeric Rating Scale (0 = no pain to 10 = worst imaginable pain); HIT-6, headache impact test-6; BMI, body mass index; B, blurred vision; D, double vision; T, tinnitus; V, visual obscurations; OCT, optical coherence tomography; RNFL, retinal nerve fiber layer; CO, constipation; HT, hair thinning; I, itch; MC, muscle cramps.

Abbreviations: MmsHD, Monthly moderate/severe headache days; MHD, Monthly headache days; OCT, Optical coherence testing; RNFL, retinal nerve fibre layer; TMP, Temporal; SUP, Superior; NAS, Nasal; INF, Inferior.

Following initiation of Erenumab, there was a significant improvement in headache burden at three months in all patients (n = 7, MmsHD fell from 14.6 (3.1) to 8.7 (2.6), p = 0.002 and total MHD reduced from 28.9 (2.0) to 16.0 (7.0), p = 0.028) (Table 1).

Of marked interest in these cases was the response when there was recurrence of ICP and papilloedema. The relapse of IIH was identified at follow up due to patients describing minimal or subjective changes in IIH symptoms (blurred vision, double vision, transient visual obscurations, tinnitus) or weight gain (Table 1) which prompted slit-lamp examination and OCT, which revealed recurrence of papilloedema (Table 1, Fig. 1). At the time of the IIH recurrence, very unexpectedly, headaches did not recur, despite being the dominant feature at initial IIH presentation and indicating exacerbations of IIH in the past. Improved headache burden was also noted at subsequent time points despite ongoing papilloedema (Fig. 1). There were no serious side effects of treatment reported at the 3-monthly assessments (over 12 months) and none of the patients withdrew from Erenumab.

**Discussion And Conclusions**

We report seven patients with IIH who had disabling long term headaches with migraine-like characteristics (mean IIH duration 2.4 (1.4) years) persisting despite complete resolution of papilloedema. Monthly headache burden was significantly reduced following initiation of a CGRP monoclonal antibody therapy. But of principle interest is the lack of headache when raised ICP retuned with recurrent papilloedema whilst they were taking a CGRP monoclonal antibody.

These cases indicate that CGRP is likely an important driver of headaches in IIH. CGRP blockade with a monoclonal antibody was associated with a significant, and persistent reduction in headache morbidity. A meaningful headache treatment response was noted both when patients were in remission (resolution of papilloedema) when they had migraine-like headaches, as well as with evidence of increased ICP (active papilloedema).
Erenumab reduced the mean frequency of MmsHD by 38% at 3 months, 49% at 6 months, 64% at 9 months and 65% at 12 months compared to baseline, with corresponding significant reductions in the total MHD and HIT-6 score, despite the recurrence of active IIH and return of papilloedema.

The mechanisms driving headache in patients with IIH have not been elucidated and treatment approaches are lacking.(1, 4, 5) Headaches in IIH are typically chronic migraine-like, drive disability and are a patient prioritised key area for mechanistic research and treatment.(3, 4, 8) CGRP is a key modulator of migraine headaches(9) and this case series provides evidence for the role of CGRP as an important nociceptive stimulus in IIH headaches. The therapeutic reduction of headache was noted in IIH patients in ocular remission, but more importantly also during the subsequent phase of recurrent active IIH, suggesting that headaches driven by raised ICP may involve CGRP release.

Exacerbation of headache is a common trigger for IIH patients to seek medical review, typically indicated recurrence of IIH and papilloedema. However, development of active papilloedema in this series of IIH patients treated with a CGRP specific agent was not associated with exacerbation of headache. Whilst the enduring control of headaches, even during a period of actively elevated ICP with papilloedema, is symptomatically advantageous to the patients there is also an important caution. In these cases, the headaches were controlled and did not recur to warn of an IIH disease relapse hence there could be a risk that relapse of IIH could be missed. Funduscopic review is typically reduced in frequency in IIH patients in whom IIH has resolved (typical follow up intervals recommended in the IIH guidelines).(10) But in IIH patients who respond to CGRP monoclonal antibody therapy for headache, we would recommend ongoing regular fundoscopy, with a low threshold for a complete neuro-ophthalmic assessment. In these cases, mild subjective changes in IIH symptoms and weight gain were markers of IIH relapse (in the absence of headache recurrence). It is important not to miss recurrence of papilloedema, as patients require visual function monitoring and management to mitigate the risk of visual loss.(6)

These cases provide the first insight that CGRP may be a key mechanistic driver for IIH headaches when raised ICP is present, manifesting as papilloedema. Headache therapies are a patient priority and an unmet need in IIH with no previous trials of headache preventative therapies in IIH.(5) CGRP may represent a therapeutic target for raised ICP IIH headaches and clinical trials investigating CGRP-specific agents would be of interest.

Clinical Implications

- CGRP monoclonal antibodies successfully treat resistant migraine-like headaches in IIH in whom their papilloedema has settled.
- CGRP has a mechanistic role in driving raised ICP headaches in active IIH.
- The therapeutic potential of CGRP monoclonal antibodies for IIH headache warrants further evaluation in a clinical trial.
Declarations

Ethics approval and consent to participate

Data for the patients involved was collected as part of a registered service evaluation University Hospitals Birmingham National Health Service Foundation Trust, United Kingdom (Registered Code, Clinical Audit Registration and Management System: CARMS-15001) with data collection approved by NHS National Research Ethics Committee (14/LO/1208), IIH:LIFE study.

Consent for publication

Written informed consent was obtained from the patient for publication of the accompanying ophthalmic images and the case report.

Availability of data and material

The data that support the findings of this case series are available from the corresponding author on reasonable request.

Competing interests

Edwards has received speaker fees and Honoraria from Novartis, Teva, Eli Lily and Allergan on headache treatments but not related to IIH. Mollan has received Honoraria from Novartis for speaking on topics unrelated to this drug, but within a National headache network meeting (November 2019). Sinclair has received speaker fees and Honoraria from Novartis (Erenumab) and Allergan (BOTOX), in addition, Invex therapeutics, company director with salary and stock options (2019, 2020). Grech, Consultancy work for Invex therapeutics (2020). Authors declare no other financial relationships with any organisations that might have an interest in the submitted work; and no other relationships or activities that could appear to have influenced the submitted work.

Funding

Lavery is supported by a Wellcome Trust Senior Fellowship (104612/Z/14/Z). Sinclair is supported by a Sir Jules Thorn Award for Biomedical Research. Grech is funded by a Brain Research UK PhD Studentship. Erenumab was funded through an NHS free of charge scheme by Novartis, UK. There was no other dedicated funding for the case series as the patients were seen as part of routine NHS clinical practice.

Authors' contributions
AY designed and conceptualized study; major role in acquisition, analysis and interpretation of data; performed statistical analysis; drafted and revised the manuscript for intellectual content.

JM designed and conceptualized study; role in acquisition, analysis, or interpretation of data; revised the manuscript for intellectual content.

VV had a role in acquisition of data; revised the manuscript for intellectual content.

OG had a role in interpretation of data; revised the manuscript for intellectual content.

EB had a role in acquisition of data; revised the manuscript for intellectual content.

GG designed and conceptualized study; role in analysis, and interpretation of data; revised the manuscript for intellectual content.

CF had a role in acquisition of data; revised the manuscript for intellectual content.

JE had a role in acquisition of data; revised the manuscript for intellectual content.

SM designed and conceptualized study; role in acquisition, analysis, and interpretation of data; revised the manuscript for intellectual content.

AS designed and conceptualized study; role in acquisition, analysis and interpretation of data; drafted and revised the manuscript for intellectual content.

**Acknowledgments**

Not applicable

**Abbreviations**

IIH, Idiopathic Intracranial Hypertension; ICP, raised intracranial pressure; CGRP, calcitonin gene related peptide; NHS, National Health Service; OCT, optical coherence tomography; MmsHD, monthly moderate/severe headache days; MHD, all monthly headache days; HIT-6, Headache Impact Test -6.

**References**

[1] Mollan SP, Davies B, Silver NC, Shaw S, Mallucci CL, Wakerley BR, et al. Idiopathic intracranial hypertension: consensus guidelines on management. Journal of Neurology, Neurosurgery & Psychiatry. 2018;89(2018):1088-100.

[2] Mollan SP, Aguiar M, Evison F, Frew E, Sinclair AJ. The expanding burden of idiopathic intracranial hypertension. Eye (Lond). 2019;33(2019):478-85.
[3] Mulla Y, Markey KA, Woolley RL, Patel S, Mollan SP, Sinclair AJ. Headache determines quality of life in idiopathic intracranial hypertension. The journal of headache and pain. 2015;16(2015):521.

[4] Mollan SP, Hoffmann J, Sinclair AJ. Advances in the understanding of headache in idiopathic intracranial hypertension. Current opinion in neurology. 2019;32(2019):92-8.

[5] Mollan S, Hemmings K, Herd CP, Denton A, Williamson S, Sinclair AJ. What are the research priorities for idiopathic intracranial hypertension? A priority setting partnership between patients and healthcare professionals. 2019;9(2019):e026573.

[6] Friedman DI, Liu GT, Digre KB. Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. Neurology. 2013;81(2013):1159-65.

[7] Sacco S, Braschinsky M, Ducros A, Lampl C, Little P, van den Brink AM, et al. European headache federation consensus on the definition of resistant and refractory migraine: Developed with the endorsement of the European Migraine & Headache Alliance (EMHA). The journal of headache and pain. 2020;21(2020):76.

[8] Mollan S, Hemmings K, Herd CP, Denton A, Williamson S, Sinclair AJ. What are the research priorities for idiopathic intracranial hypertension? A priority setting partnership between patients and healthcare professionals. BMJ open. 2019;9(2019):e026573.

[9] Tepper S, Ashina M, Reuter U, Brandes JL, Dolezil D, Silberstein S, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol. 2017;16(2017):425-34.

[10] Mollan SP, Davies B, Silver NC, Shaw S, Mallucci CL, Wakerley BR, et al. Idiopathic intracranial hypertension: consensus guidelines on management. J Neurol Neurosurg Psychiatry. 2018(2018).

Figures
Figure 1

Headache days, BMI and optical coherence testing of patients A. Monthly moderate/severe headache days (MmsHD) at clinical assessment timepoints. Each patient is represented by different colour. Relapse point is represented by empty circle or triangle large point for each patient. B. Mean number of monthly moderate/severe headache days (MmsHD) and total monthly headache days (MHD) at -12 months, baseline and at relapse. Error bars represent standard error of the mean (SEM). T-test performed for changes compared to baseline for MmsHD and Wilcoxon signed ranks test performed for changes compared to baseline for MHD. ***P < 0.001 compared to baseline, ** P < 0.01 compared to baseline, * P < 0.05 compared to baseline. C. Body mass index percentage change at time of relapse compared to baseline (significant fluctuations in weight were possible in between formal clinical assessments, but
were not measured). Each patient is represented by different colour. D. Optical coherence tomography (OCT) global average peripapillary retinal nerve fibre layer (pRNFL) thickness at clinical assessment timepoints. Each patient is represented by different colour. E. Infrared image of the right eye at baseline (Heidelberg Engineering SPECTRALIS, Heidelberg, Germany) for Patient 2 (P2). This shows no papilloedema. F. Infrared image of the right eye at 6 months Patient 2 (P2). This shows recurrence of papilloedema. G. Graph of OCT cross-sectional pRNFL thickness derived from 12-ring scan centred on the optic disc (Heidelberg Engineering SPECTRALIS, Heidelberg, Germany). Black line shows the cross-sectional pRNFL thickness of the six-month scan (relapse), with the grey line showing the same information for the baseline scan. The difference between these lines (red arrows) indicates the magnitude of increase in pRNFL thickness between these scans, demonstrating relapse of IIH and recurrence of active papilloedema. The shaded green area indicates the proprietary ‘normal’ range for pRNFL thickness. Abbreviations: MmsHD, Monthly moderate/severe headache days; MHD, Monthly headache days; OCT, Optical coherence testing; RNFL, retinal nerve fibre layer; TMP, Temporal; SUP, Superior; NAS, Nasal; INF, Inferior.