



# Locking down the CGRP pathway during the COVID-19 pandemic lockdown: the Pandemig study

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## Abstract

**Objectives** The COVID-19 pandemic and the consequent lockdown came as a storm disrupting people's everyday life. This study aimed at observing whether the COVID-19 related lockdown influenced migraine frequency and disability in migraine patients on therapy with monoclonal antibodies inhibiting the CGRP pathway.

**Methods** In this longitudinal observational cohort study, 147 consecutive patients receiving monthly administration of erenumab or galcanezumab were enrolled in four Italian headache centers. All patients filled a questionnaire concerning working and household settings, recent flu symptoms or COVID-19 diagnosis, and family loss due to COVID-19 infection. Monthly migraine days (MMDs), monthly painkiller intake (MPI), and HIT-6 disability relative to the first month of lockdown imposition (T-lock) and the month before (T-free) were also collected.

**Results** From T-free to T-lock, the cohort displayed a reduction in MMDs (from  $10.5 \pm 7.6$  to  $9.8 \pm 7.6$ ,  $p = .024$ ) and HIT-6 scores (from  $59.3 \pm 8.3$  men reduced MPI more frequently than women ( $p = .005$ ).

**Conclusions** Our study observed that the lockdown impact to  $57.8 \pm 8.8$ ,  $p = .009$ , while MPI resulted unchanged (from  $11.6 \pm 11.5$  to  $11.1 \pm 11.7$ ;  $p = .114$ ). MMDs, MPI, and HIT-6 variations from T-free to T-lock did not differ according to work settings or household. Patients beyond the first 3 months of therapy presented less often a reduction in MMDs ( $p = .006$ ) and on everyday life did not affect the migraine load in patients receiving monoclonal antibodies inhibiting the CGRP pathway. Patients in the first months of therapy experienced a greater improvement according to drug pharmacokinetics, while women more frequently needed rescue medications, possibly indicating presenteeism or cephalalgophobia.

**Keywords** Migraine · CGRP · COVID-19 · Erenumab · Galcanezumab

## Introduction

Since March 11th, the imposition of the emergency lockdown related to COVID-19 diffusion disrupted the everyday life of Italian Citizens, including patients affected by migraine. Lifestyle, everyday habits, and stressful conditions influence greatly migraine frequency [1, 2].

The quarantine was a unique condition to investigate the impact of changing the routine life on migraine. Daily habits, however, were disrupted by the lockdown very variably depending on the condition of social isolation, work settings, reduced income, or the necessity to match one's work needs with children's demands including digital education.

This study aimed at observing whether the lockdown influenced migraine frequency (monthly migraine days—MMDs) and disability (HIT-6 scores) in patients receiving monoclonal

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antibodies inhibiting the CGRP pathway. We hypothesized that the social, family organizational, and economic consequences of the lockdown strongly influenced the migraine burden.

## Methods

This is an observational longitudinal cohort study. It was conducted as part of two ongoing observational longitudinal multicentric studies on the real-life use of erenumab (the EARLY—ErenumAb in Real Life in Italy—study) and galcanezumab (the GARLIT—GalcanezumAb in Real Life in Italy—study), two monoclonal antibodies inhibiting the CGRP pathway, in different headache centers across Italy. The EARLY [3] and GARLIT [4] studies investigate the effectiveness of erenumab or galcanezumab, prescribed upon clinical indication [5], by prospectively collecting monthly migraine days (MMDs), monthly painkiller intake (MPI), and monthly disability scale (i.e., Headache Impact Test—HIT-6, Italian version 1.1). All patients were educated on the headache diary use at the beginning of the GARLIT and EARLY studies.

The present study aimed at assessing whether MMDs, MPI, and HIT-6 in the first month since lockdown imposition (T-lock) differed from the month before (T-free). We also investigated the effect of working and household situations, or COVID-19 related issues on MMDs, MPI, and HIT-6 variations.

From April 11 to May 11, 2020, we proposed to participate to the PandeMig study all consecutive migraine patients taking part in the EARLY and GARLIT studies and able to attend the scheduled visit during T-lock. In 2 headache centers in Lazio region (Central Italy) and 2 headache centers in Emilia-Romagna region (Northern Italy), they all agreed. To investigate current work and household situation and flu symptoms or COVID diagnosis, all participants were invited to fill a questionnaire we had set up (Table 1). Given the sudden emergency, we could not validate the questionnaire before the study beginning.

We calculated the absolute variations of MMDs, MPI, and HIT-6 scores as T-lock minus T-free values and defined as “improving” (as a binary variable) any reduction in HIT-6 scores, MMDs, and MPI.

The study was approved by the Campus Bio-Medico University Ethical Committee (prot 6/19 OSS ComET CBM). All participants provided written informed consent. Anonymized data will be shared upon request from any qualified investigator.

## Statistical analysis

To detect a small effect size of .25 between pairs of repeated measures and to achieve a power of 80% and a level of significance of 5% (two-sided), we calculated a sample size of at

**Table 1** Work, household and COVID related issues questionnaire

Question	
Working status (Q1)	
Since lockdown:	a. I take advantage of smart working b. I go to work c. I had economic losses d. I was unemployed/retired before lockdown
Household (Q2)	
At home	a. I live alone b. I live with my partner/family c. I live with family and kids
Family loss (Q3)	
Did you lose any family member because of COVID-19?	a. Yes b. No
Flu symptoms (Q4)	
Did you have flu symptoms?	a. Yes b. No
COVID-19 diagnosis (Q5)	
Were you diagnosed COVID-19?	a. Yes b. No

least 128 subjects. This is the primary a priori analysis of the collected data.

Statistical analyses were performed using SPSS 25.0, SPSS Inc., Chicago, IL, USA. Differences were considered significant at the  $p < .050$  level. Data distribution was assessed by the Kolmogorov-Smirnov test. Variables non-normally distributed were compared with the Mann-Whitney  $U$  test (between groups) or Friedman analysis of rank (within-group). The two-tailed Fisher exact test was used for dichotomous variables. Binary logistic regression was run to assess which factors (exposures) among working and household settings and long standing-therapy were associated with HIT-6, MMDs, or MPI improvement (outcomes).

## Results

The study cohort consisted of 147 patients; of these, 78 patients were enrolled in Lazio (53.1%) and 69 in Emilia-Romagna centers (46.9%). Before initiating the treatment with erenumab or galcanezumab, 105 out of 147 patients (71.4%) were affected by chronic migraine (CM) and the remaining 42 (28.6%) by high-frequency episodic migraine (EM). Patients were on average at the sixth administration of therapy (min-max: 2–13). Table 2 summarizes patients' characteristics.

All variables were non-normally distributed. Data were fully available for all patients. Only one patient from Emilia-Romagna was diagnosed with COVID-19 (Q5) while 5% of patients had recent flu-like symptoms (Q4), and 11.6% of

**Table 2** Patient characteristics

	T-free	T-lock	<i>p</i>
Sex (F, %)	77.6		
Age (mean, SD)	49.3 (10)		
MMDs (mean, SD)	10.5 (7.6)	9.8 (7.6)	.024
HIT-6 (mean, SD)	59.3 (8.3)	57.8 (8.8)	.009
MPI (mean, SD)	11.6 (11.5)	11.1 (11.)	.114

patients had a family member loss because of COVID-19 (Q3). Given the low prevalence of flu-like symptoms and COVID-19 diagnosis, these issues were not included in the regression analysis. Figure 1 summarizes the answers to Q1 and Q2. At T-lock, 76.2% of patients had received at least three administrations of erenumab or galcanezumab reflecting the pharmacokinetic steady-state ([www.ema.europa.eu](http://www.ema.europa.eu)).

From T-free to T-lock, the entire cohort displayed a small reduction in MMDs ( $p = .024$ ) and HIT-6 scores ( $p = .009$ ), while MPI did not change ( $p = .114$ , Table 2). MMDs, MPI, and HIT-6 variations from T-free to T-lock did not differ according to work settings (Q1), household (Q2) or COVID-19 related family loss (Q3) and the Italian region (consistently  $p > .1$ ). Nevertheless, we observed a reduction in MMDs ( $-3.69 \pm 5.20$  compared with  $.29 \pm 4.97$ ;  $p < .0001$ ), MPI ( $-3.03 \pm 6.81$  compared with  $.29 \pm 7.07$ ;  $p = .014$ ), and HIT-6 scores ( $-3.66 \pm 7.97$  compared with  $-.69 \pm 7.35$ ;  $p = .024$ ) mainly in patients who had received less than three administrations. Moreover, MMDs decreased mainly in patients affected by CM ( $-1.09 \pm 6.09$ ) compared with EM patients ( $.05 \pm 3.10$ ,  $p = .046$ ) while the reduction in MPI was higher in men ( $-1.8 \pm 4.7$ ) than in women ( $-.09 \pm 7.95$ ,  $p = .018$ ).

Table 3 summarizes the results of binary logistic regression analysis showing that patients beyond the first three months of therapy (i.e., steady-state) presented less often a reduction in MMDs. After Bonferroni correction for the 5 multiple

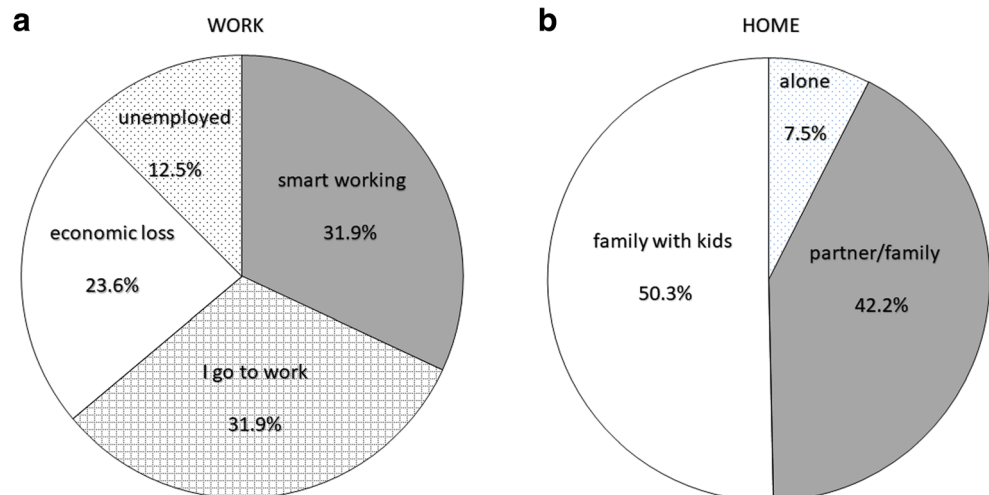
comparisons, the statistical significance was  $p = .042$ . Table 4 summarizes the results of binary logistic regression analysis displaying that the reduction in MPI was less frequent in women than in men. After Bonferroni correction for the 6 multiple comparisons,  $p$  was  $.027$ . The same analysis was run to identify variables associated with the reduction in HIT-6 score, obtaining an effect of sex ( $p = .038$ ) and therapy steady-state ( $p = .011$ ), which, however, was not significant after Bonferroni correction.

## Discussion

Despite the dramatic storm hitting the everyday lives of Italian citizens, in the present study, we observed, somehow unexpectedly, that the COVID-19 pandemic lockdown substantially spared its impact on a cohort of migraine patients receiving therapy with monoclonal antibodies inhibiting the CGRP pathway. Specifically, subjects in the first months of therapy indeed experienced an improvement in MMDs and related disability, in line with clinical trials showing that erenumab and galcanezumab are rapidly effective on migraine [6, 7]. On the other hand, an increase in migraine attacks as a reaction to the strong change of external circumstances was not observed either in patients whose CGRP pathway has blocked for 3 months or longer. Transformed work settings or copying with family caregiving seem not to influence negatively MMDs. Besides, although in Emilia-Romagna during the early phase of the pandemic were observed almost four times the COVID-19 cases registered in Lazio, ([www.epicentro.iss.it/coronavirus/](http://www.epicentro.iss.it/coronavirus/)) patients from the two regions displayed similar trends.

The lockdown was a real challenge for migraineurs. Beyond the negative emotions raised by the concerns on their own health and by the limitation of their individual freedom, they may have met further difficulties to adapt to the new daily living setting. Psychological studies showed that patients with migraine present subtle impairment of cognitive executive

**Fig. 1** **a** Percentage distribution of answers to question 1. **b** Percentage distribution of answers to question 2



**Table 3** Binary logistic regression analysis on MMDs reduction from T-free to T-lock

	B	S.E.	Wald	df	Sign	Exp (B)	95% C.I. per EXP(B)	
							Lower	Upper
Sex	-.582	.434	1.796	1	.180	.559	.239	1.309
Age	-.002	.018	.013	1	.910	.998	.963	1.034
Chronic Migraine	.008	.399	.000	1	.984	1.008	.461	2.204
Work—Q1	-.329	.178	3.415	1	.065	.720	.508	1.020
Household—Q2	.493	.287	2.940	1	.086	1.637	.932	2.874
Steady-state	-1.210	.446	7.349	1	.007	.298	.124	.715
Costant	1.011	1.315	.591	1	.442	2.748		

S.E. standard error, *df* degrees of freedom, *Sign* significance

functions (e.g., set-shifting) that can limit their ability to cope with changes of daily routine [8]. These dysfunctions were also proved to increase migraine disability [9].

It is difficult to discriminate if the effect of CGRP inhibition on migraine burden in our patients relays on central or peripheral pain mechanisms [10]. Interestingly, a recent study showed in mice that the injection of CGRP antibodies, but not by sumatriptan, could prevent migraine-like behavior and allodynia elicited by repetitive stress suggesting a central action [11]. This observation also confirms experimentally that stressful conditions may generate migraine attacks, which can effectively be prevented by inhibition of the CGRP pathway [12].

A less persuasive hypothesis is that indeed that the lockdown-related distress did not provoke migraine attacks in these patients because stress induced also corticotrophin-releasing hormone with a prevalent protective role as hypothesized in other conditions [13]. Unexpectedly, migraine onset can be associated with a decline in perceived stress [13, 14]. If so, we should expect an exacerbation of attacks once the COVID-19 social and economic crisis will have definitely calmed down. To prove this hypothesis, long-term follow-up data are necessary.

Although we did not find an influence of work-related issues on MMDs, MPI, and HIT-6 scores variation from T-free to T-lock, another possible explanation for the sustained clinical benefit during the lockdown is that even in subjects still

going to work, the workload was reduced allowing a period of relative quiet. This hypothesis is in line with the observation of ease of migraine symptoms during the quarantine despite a moderate level of depression, in a survey on a smaller cohort of Italian patients performed by telephone interview [15].

Another interesting finding in our cohort is that women did not reduce painkiller intake despite a reduction in migraine days and perceived disability. An interpretation of this finding is that women recurred more often to additional rescue medications or even to a preventive intake of painkillers due to cephalalgophobia and the urge to feel prepared to manage the increased household and family demands, in addition to their working activity. Presenteeism and the fear of pain are well-known phenomena characterizing migraineurs [16, 17]. The experience of recurrent severe pain may produce, on one hand, anticipation anxiety for the forthcoming headaches and their consequence in terms of loss of daily activities or, on the other hand, the resignation to having to perform daily activities despite the pain. Both conditions predispose to migraine overtreatment. Interestingly, an Italian study by “Istituto Superiore di Sanità” demonstrated that women lose less working days and have more working days with headache than men [18].

The main limitation of this study is the lack of a control group. However, the sudden and fast evolution of the COVID-19 pandemic did not let us to collect MMDs, MPI, and HIT-6 scores related to the month preceding lockdown in patients

**Table 4** Binary logistic regression analysis on MPI reduction from T-free to T-lock

	B	S.E.	Wald	df	Sign	Exp (B)	95% C.I. per EXP(B)	
							Lower	Upper
Sex	-1.209	.435	7.730	1	.005	.298	.127	.700
Age	.010	.018	.335	1	.563	1.010	.976	1.046
Work—Q1	-.029	.172	.028	1	.868	.972	.693	1.362
Household—Q2	.020	.278	.005	1	.943	1.020	.591	1.760
Steady state	-.722	.412	3.080	1	.079	.486	.217	1.088
Costant	.941	1.247	.570	1	.450	2.563		

S.E. standard error, *df* degrees of freedom, *Sign* significance



under different preventive therapies outside our ongoing interventional studies. Indeed, the lockdown involved also ordinary healthcare services since only urgent visits were allowed.

In conclusion, our study observed that patients receiving monoclonal antibody inhibiting the CGRP pathway were not affected by the lockdown impact on everyday life. Patients in the first months of therapy experienced a greater improvement according to drug pharmacokinetics. On the other side, despite the good control of migraine frequency, women more frequently needed rescue medications indicating presenteeism or cephalalophobia.

**Data availability** Anonymized data will be shared by request from any qualified investigator.

### Compliance with ethical standards

**Conflict of interest** Claudia Altamura received travel grants from Novartis, Lusofarmaco, Laborest. Sabina Cevoli received honoraria as speaker panels, for participating in advisory boards from Teva, Allergan, and Novartis. Cinzia Aurilia received travel grants from Eli-Lilly, FB-Health, Lusofarmaco, and Teva. Gabriella Egeo received travel grants and honoraria from Eli-Lilly, Novartis, New Penta, and Ecupharma. Luisa Fofi received travel grants and honoraria for the advisory board from Teva, Eli-Lilly, and Novartis Paola Torell received travel grants and honoraria from Allergan, Teva, Eli-Lilly and Novartis Giulia Pierangeli received honoraria as a speaker, for participating in advisory boards or for investigation studies from Teva, Allergan, Novartis, Electrocore Valentina Favoni received honoraria as a speaker or for participating in advisory boards from Ely-Lilly, Novartis and Teva. Piero Barbanti honoraria for advisory boards, speaker panels, or investigation studies from Alder, Allergan, Bayer, ElectroCore, Eli-Lilly, GSK, Lusofarmaco, MSD, Novartis, Stx-Med, Teva, Visufarma. Fabrizio Vernieri received travel grants, honoraria for advisory boards, speaker panels, or clinical investigation studies from Allergan, Angelini, Eli-Lilly, Novartis, Teva. Nicoletta Brunelli, Adriana Falllacara, and Umberto Pensato have no conflict to report.

**Ethics approval** The study was approved by the Campus Bio-Medico University Ethical Committee (prot 6/19 OSS ComET CBM).

**Consent to participate** All participants provided written informed consent

**Consent for publication** All authors provided consent for publication of the manuscript in the current form in Neurological Science.

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