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Effectiveness of transcranial direct current stimulation and monoclonal antibodies acting on the CGRP as a combined treatment for migraine (TACTIC): Results of a randomized controlled trial

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Abstract

Background: Migraine pathogenesis involves both central and peripheral mechanisms. Although calcitonin gene-related peptide monoclonal antibodies have shown efficacy over placebo in migraine prevention, a proportion of individuals with migraine may experience a substantial residual burden while on treatment. Transcranial direct current stimulation is a non-invasive neuromodulation technique that can target central migraine mechanisms and may therefore complement calcitonin gene-related peptide monoclonal antibodies. The present study aimed to assess the efficacy of transcranial direct current stimulation as an adjunctive treatment to calcitonin gene-related peptide monoclonal antibodies in migraine prevention and to investigate its neurophysiological effects.

Methods: This is a multicenter, randomized double-blind, sham-controlled, parallel-group trial including subjects with migraine on treatment with calcitonin gene-related peptide monoclonal antibodies for ≥90 days and with ≥8 monthly migraine days in the last 30 days. Subjects were randomized to active or sham transcranial direct current stimulation. The transcranial direct current stimulation protocol consisted of five daily 20-minute sessions of bilateral cathodal stimulation on the occipital area and anodal stimulation on the M1 area. High-density electroencephalographic recordings were performed before the first and after the last transcranial direct current stimulation session. The primary endpoint was the number of headache days during the 28-day follow-up period controlling for the 28-days baseline value. Secondary endpoints included the number of migraine days during the follow-up period, disability measures and electroencephalographic spectral power. The active and sham groups were compared using analysis of covariance. For clinical outcomes with significant differences between groups, we also ran paired *t*-tests comparing baseline and follow-up assessment within groups.

Results: Thirty participants were randomized (15 to active and 15 to sham group). Headache days during the 28-day follow-up period did not differ significantly between groups ($p = 0.560$, $\eta_p^2 = 0.017$). However, participants receiving active transcranial direct current stimulation reported fewer migraine days during follow-up compared to the sham group ($p = 0.008$, $\eta_p^2 = 0.241$). Paired *t*-tests indicated that the active tDCS group reported a reduction in migraine

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days during the follow-up period compared to baseline ($t = 2.557$, $p = 0.023$, Cohen's $d = 0.660$), while no difference was found in the sham group. Referring to neurophysiological endpoints, active transcranial direct current stimulation induced a significant decrease in delta power at frontal regions compared to sham.
Conclusions: This randomized-controlled trial suggests that transcranial direct current stimulation is a promising potentially effective treatment that may give additional benefits to subjects with migraine who are already on prevention with calcitonin gene-related peptide monoclonal antibodies but who have a substantial residual migraien burden. Combination treatments need to be better explored to provide strategies to further improve benefits of migraine prevention.
Trial Registration: NCT05161871 (clinicaltrials.gov).

Keywords
migraine, monoclonal antibodies, neuromodulation, refractory migraine, resistant migraine, transcranial direct current stimulation

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Introduction

With a prevalence of about one billion sufferers worldwide (1), migraine ranks third among the causes of disability due to diseases of the nervous system (2). The pathogenesis of migraine includes both central and peripheral mechanisms. Central mechanisms typical of migraine include cortical spreading depression (CSD), which is considered the neurobiological basis of migraine aura (3,,–5), lack of habituation to external stimuli during the interictal period (i.e., the period between two different attacks) (6,7), and several alterations in the connectivity of cortical and subcortical structures, including the thalamus, hypothalamus, brainstem and amygdala, which may be involved in the modulation of pain and sensory function (8). The so-called "thalamocortical dysrhythmia" (i.e., an alteration of the normal connection between the thalamus and the cortex) has been reported in individuals with migraine (9,10), as well as in those with other pain conditions (11,,–13). Peripheral mechanisms of migraine include the activation of the trigeminovascular complex (5,14) and the consequent release of many mediators of pain, including calcitonin gene-related peptide (CGRP), from the meninges (14). Central and peripheral mechanisms are likely linked, as CSD has been found to activate trigeminal fibers, which in turn release pain-inducing peptides and mostly CGRP (5).

The discovery of migraine-specific preventive treatments stemmed from the discovery of CGRP and of its roles in the pathogenesis of migraine attacks. Monoclonal antibodies targeting the CGRP pathway (anti-CGRP/R mAbs) and gepants are all inhibitors of CGRP or of its receptor in the trigeminovascular system. Those drugs proved effective in migraine prevention with a favorable tolerability profile (15). Nevertheless, they do not cross the blood–brain barrier (16) and therefore do not act on central mechanisms of migraine. Besides, a relevant proportion of individuals with migraine do not respond to this drug class (17). Even individuals with a substantial response to those drugs might have a high number of residual monthly migraine days (18). Individuals who do not adequately respond to peripherally acting drugs constitute an interesting opportunity to study central mechanisms of migraine, as in those individuals central mechanisms prevail on peripheral ones. Notably, it has been shown in a clinical model that some migraine attacks are CGRP-independent (19).

As pharmacological treatment for migraine is not always viable due to potential contraindications, poor effectiveness or adverse events, it can be replaced or integrated with non-pharmacological methods. Neuromodulation techniques, such as transcranial direct current stimulation (tDCS), have gained momentum in the treatment of migraine and other chronic pain conditions (20,21) and can be used in patients who prefer non-pharmacological management or who cannot be adequately managed with drugs. tDCS is a non-invasive and painless technique of neuromodulation, consisting in the delivery of a weak current (1–2 mA) through the scalp via electrodes applied on the skin and connected to a battery-driven stimulator; the aim of tDCS is to modulate spontaneous neuronal firing rate by the polarization of resting membrane potential (22). Anodal stimulation increases cortical excitability by depolarizing neurons in the stimulated area, while cathodal stimulation hyperpolarizes neurons with inhibitory effects (23).

Because tDCS acts, as far as is known, predominantly on central mechanisms of migraine, while anti-CGRP/R mAbs pathway act peripherally on the trigeminovascular system, using tDCS as an add-on to anti-CGRP/R mAbs could be a viable option to potentiate the efficacy of those drugs. Additionally, the known effects of both monoclonal antibodies targeting the CGRP pathway and tDCS allow to study some of migraine mechanisms *in vivo*.

The present randomized controlled trial had a clinical and neurophysiological dual objective. The clinical objective was to assess whether the addition of tDCS could

improve the efficacy of the treatment with anti-CGRP/R mAbs by reducing several migraine endpoints: frequency, intensity, acute medication use, migraine-related disability, quality of life, sleep disturbance and psychological symptoms compared to a sham procedure. The neurophysiological objective was to provide information on the cortical mechanisms underlying the possible improvement in efficacy of the tDCS/ anti-CGRP/R mAbs integrated approach by describing the acute electroencephalographic (EEG) changes induced by the stimulation protocol.

Methods

This is a multicenter randomized double-blind, sham-controlled, parallel-group trial. The study was approved by the Ethics Committee for the districts of L'Aquila and Teramo with Protocol Number 272/21 and registered in Clinicaltrials.gov with the code NCT05161871. All patients provided their written informed consent to participate in the study. Details on the study protocol are published elsewhere (24). With respect to the original protocol, two differences were applied as an amendment:

1. The trial became multicenter with the addition of the "C. Mondino" Neurological Institute of Pavia
2. Participants' inclusion was allowed even after 180 days since starting treatment with monoclonal antibodies

Inclusion and exclusion criteria

Our trial followed the guidelines issued by the International Headache Society for neuromodulation in headaches (25). The inclusion criteria were the following:

- male or female individuals with migraine, aged between 40 and 70 years, referring to the Headache Centers of the University of L'Aquila and of the "C. Mondino" Neurological Institute of Pavia (Figure 1)
- a diagnosis of migraine with or without aura according to the International Classification of Headache Disorders (26)
- migraine present for at least 12 months
- subjects were being treated with anti-CGRP/R mAbs (erenumab, fremanezumab or galcanezumab) for ≥90 days since the first subcutaneous administration (this time range was chosen to ensure a stable CGRP pathway inhibition)
- subjects reporting ≥8 monthly migraine days in the last 30 days of observation despite treatment with anti-CGRP/R mAbs

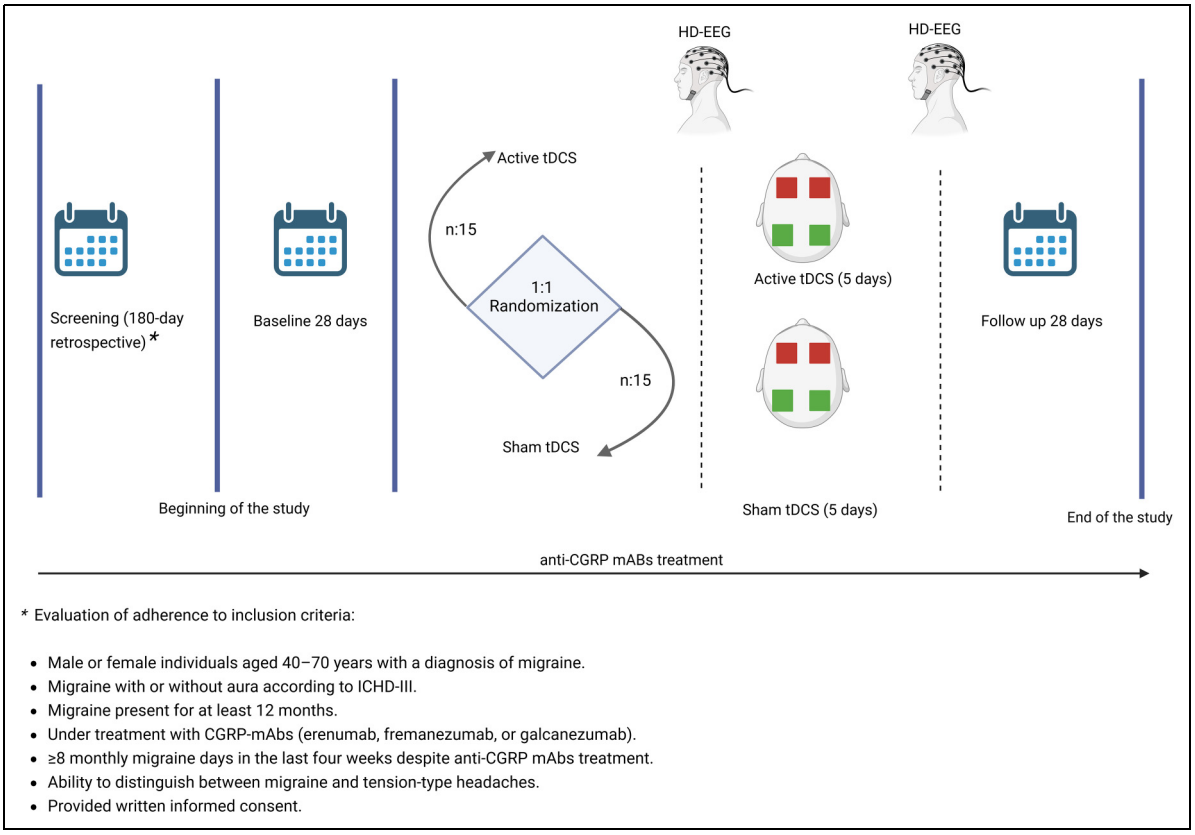

Figure 1. Schematic representation of trial procedures. Anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs) indicates monoclonal antibody; HD-EEG, high-density electroencephalogram; tDCS, transcranial direct current stimulation. For the transcranial direct current stimulation, green squares indicate the cathodes, while red squares indicate the anodes.

- subjects able to discriminate between migraine and tension-type headaches
- written informed consent to participate in the study

Treatment with anti-CGRP/R mAbs was prescribed according to Italian reimbursement criteria, namely in individuals with migraine reporting ≥8 monthly migraine days with a Migraine Impact and Disability Assessment Scale score ≥11 and having failed at least three preventive medication classes among beta-blockers, tricyclic antidepressants, anticonvulsants and onabotulinumtoxinA.

Individuals with other concomitant primary headache types were included if attacks of those other headaches were <1 day/month and <12 days/year.

Subjects with medication overuse headache and menstrually-related migraine were not excluded from the study. We did not report subgroup analyses for those subjects because the analyses would have been underpowered.

The exclusion criteria were the following:

- use of any concurrent migraine preventive medication other than anti-CGRP/R mAbs;
- secondary migraine-like headache
- epilepsy or any other neurologic condition that may be worsened by transcranial electrical stimulation
- metallic head implants, cardiac pacemaker or any other device that could malfunction or be displaced by electrical stimulation
- pregnancy or lactation

Migraine preventive treatments other than anti-CGRP/R mAbs had to be withdrawn for at least 60 days before inclusion in the trial.

Visit schedule and assessment

The study included a 90-day retrospective screening period, a 28-day prospective baseline period, a 5-day stimulation period and a 28-day follow-up period. Participants were enrolled over a 24-month period from January 2022 to December 2023.

After providing their informed consent, participants' baseline characteristics were recorded, including age, race, ethnicity, and relevant physiological and medical history. Prior headache characteristics and previous headache medication history were also collected.

Randomization and blinding

Participants were randomly assigned in a 1:1 ratio to active or sham tDCS. Randomization was performed by one of the investigators (AdA) who was unaware of personal data of study participants. The allocation sequence was generated in a MATLAB (MathWorks Inc., Natick, MA, USA) environment. The investigators who administered the stimulation protocol (CR, FdS, AO, VG, FC, FB and MC), as well as participants, were blinded to the type of stimulation applied (double blind). Endpoint assessment was performed by an investigator (AdA) who was aware of the treatment performed, but not of the participants' clinical data. We did not include a tDCS-only arm in the study because the trial was focused on the combination of neuromodulation with blockade of the CGRP pathway rather than on the effect of neuromodulation itself.

Baseline visit

Screened subjects underwent a 28-day baseline period to confirm their eligibility, by filling out a headache diary containing information about headache occurrence, its intensity on a numerical rating scale of 1–10, its duration (hours), associated symptoms (nausea, vomiting, photophobia, phonophobia) and consumption of drugs for the acute treatment. Participants also had to fill out the following questionnaires to assess migraine-related disability, quality of life, sleep disturbance and psychological aspects: modified Migraine Disability Assessment (mMIDAS); Headache Impact Test-6 (HIT-6); Pittsburgh Sleep Quality Index (PSQI) and Hospital Anxiety and Depression Scale (HADS).

Stimulation protocol

tDCS was administered by trained personnel. The stimulation protocol consisted in five daily sessions lasting 20 minutes of a bilateral cathodal stimulation on the occipital area, with the reference anodal electrodes positioned on the M1 area. The stimulation was applied via four conductive-rubber square electrodes (5×5 cm) placed in sponges saturated with high conductivity gel and connected to a battery-operated stimulator system (BrainSTIM; EMS Medical, Bologna, Italy). In the active tDCS group, a direct current with maximal intensity of 1.5 mA was delivered for 20 minutes (30 seconds ramp-in/ramp-out). In the sham group, the current was turned off after 10 seconds (30 seconds ramp-in/ramp-out) at the beginning and at the end of the 20-minute interval, aiming to maintain the same tingling sensation that subjects experience during the gradual increase/decrease of the current intensity at the beginning/end of the 'verum' stimulation procedure. Patients filled out the headache diary during the 5 days of tDCS. Patients continued their anti-CGRP drug treatment during the whole study period.

EEG recording and pre-processing

Patients performed a 5-minute resting EEG recording with eyes closed, immediately before the first and immediately after the last tDCS session. EEG signals at Headache Centers of the University of L'Aquila were recorded via 64 active electrodes mounted on an elastic cap (ActiCAP)

connected to a BrainAMP RM amplifier (Brain Products GmbH, Gilching, Germany) with a sampling rate of 500 Hz. EEG signals at "C. Mondino" Neurological Institute of Pavia were recorded via 128 active electrodes mounted on an elastic net (HydroCel Geodesic Sensor Net; Electrical Geodesics, Inc., Eugene, OR, USA) connected to an amplifier with sampling rates of 500 or 1000 Hz.

EEG traces were pre-processed offline using the EEGlab toolbox, version 2021 (Swartz Center for Computational Neuroscience, San Diego, CA, USA) working on MATLAB R2020b (MathWorks Inc.).

To ensure standardization, the 128 EEG channels from "C. Mondino" Neurological Institute of Pavia were reduced to 64 channels, selecting the cortical sites overlapping with the 10-10 montage adopted at the University of L'Aquila. Preliminary tests were performed to standardize EEG recording between the two centers.

All EEG data recordings were downsampled at 250 Hz, high pass filtered at 0.5 Hz, low pass filtered at 30 Hz and re-referenced to the average of the mastoids (TP9 and TP10 sites in 10-10 international system). Ocular and muscular artifacts were corrected via independent component analysis on continuous data and channels with excessive noise or poor skin contact were interpolated. A visual check excluded further portions of the signals with residual artefacts. Power spectra were computed via fast Fourier transform on 2 seconds artefacts free epochs with a Hanning window, 50% overlap and a bin resolution of 0.50 Hz. The spectral power in each frequency band was obtained by averaging the power of adjacent bins in the ranges: 1–4.5 Hz (delta), 5–8.5 Hz (theta), 9–12.5 Hz (alpha) and 13–25.5 Hz (beta).

Follow-up

Patients underwent a 28-day follow-up assessment period starting from the day following the last tDCS session, filling out a diary identical to those of the baseline period. At the end of the follow-up period, patients filled out the same questionnaires as during the baseline period. To verify blindness, patients were also asked whether they received active or sham tDCS.

Efficacy endpoints

The primary efficacy endpoint was the number of headache days during the 28-day follow-up period corrected for the baseline period value. Secondary endpoints included the number of migraine days, acute treatment consumption (doses), migraine-related disability (mMIDAS score) and impact (HIT-6 score), sleep quality (PSQI score), and anxious and depressive symptoms (HADS-A and HADS-D score) during the 28-day follow-up period. An additional neurophysiological endpoint was the the spectral power in the delta (1–4.5 Hz), theta (5–8.5 Hz), alpha (9–12.5 Hz) and beta (13–25.5 Hz) frequency bands in the EEG measurement at the end of the stimulation protocol. A headache day was defined as any day on which a participant reported any headache lasting at least 4 hours, regardless of its characteristics. A migraine day was defined as a day with a headache lasting at least 4 hours that met the International Classification of Headache Disorders, 3rd edition (ICHD-3) criteria C and D for migraine without aura (1.1), criteria B and C for migraine with aura (1.2) or the criteria for probable migraine (1.6). Additionally, a day on which a headache was successfully treated with a triptan, ergotamine, or other migraine-specific acute medication was also considered a migraine day. Migraine days were included in the count of headache days.

Safety endpoints

Safety assessment included adverse event reporting. Adverse event monitoring was performed during the 5-day tDCS stimulation sessions and during the 28-day follow-up period after tDCS. Adverse events were detected and collected by investigators with a standard questionnaire (27) and open-ended questions. Monitoring for serious adverse events was performed according to common clinical practice.

Statistical analysis

Continuous data were summarized as the mean ± SD. Categorical data are presented as numbers and proportions.

Independent samples *t*-tests and chi-squared tests were used to evaluate potential baseline differences between the experimental groups (active/sham) on demographic (sex and age) and clinical variables (headache days, migraine days, consumption of acute treatments, headache-related disability and questionnaire scores).

To evaluate the effect of tDCS, groups (active/sham) were compared on clinical variables at the follow-up assessment using analysis of covariance (ANCOVA) with baseline values as covariate (28,29) For clinical endpoints reporting significant differences between groups, paired *t*-tests were also performed directly comparing baseline and follow-up assessment within groups.

Similarly, EEG spectral powers at the end of the stimulation protocol were compared between groups via ANCOVA with baseline values as covariates. The statistical significance of the differences in spectral power was controlled via false discovery rate (FDR) accepting only differences associated with $Q < 0.05$ (30), separately for each frequency band.

The changes in spectral powers for the frequency bands and cortical sites showing a significant tDCS effect were then correlated (Pearson's *r*) to the degree of response to the treatment for clinical variables showing a significant

effect to assess possible relationship between clinical and neurophysiological endpoints.

Finally, to provide more detailed evidence of the effect of tDCS on the cortical physiology of the participants, we assessed significant EEG power changes in the active tDCS group, directly comparing the spectral powers in each frequency band at the end of the stimulation protocol with those recorded at baseline via paired *t*-tests with FDR correction.

The potential association between treatment (active/sham) and incidence of adverse events was evaluated using chi-squared tests.

Sample size

The sample size calculation was performed using G*Power, version 3.1 (31). According to previous literature (32), a between-groups mean difference of 3 ± 2 migraine days/month was considered significant. The computation was made with the following parameters: confidence interval (two-sided): 95%; power: 80%; ratio of sample size: 1:1; mean change in group 1: −4 days; mean change in group 2: −1 day; SD: 2. The minimum sample size suggested was of 9 patients per group. In consideration of possible dropouts, we set our population size to 30 patients, with 15 per group.

Data availability

The dataset is not publicly available because their dissemination could compromise the privacy of participants.

Results

During the study period, we included 30 participants out of 53 screened subjects; the CONSORT flowchart is reported in Figure 2. The two treatment cohorts were balanced with regard to the baseline characteristics (Table 1); 12 patients

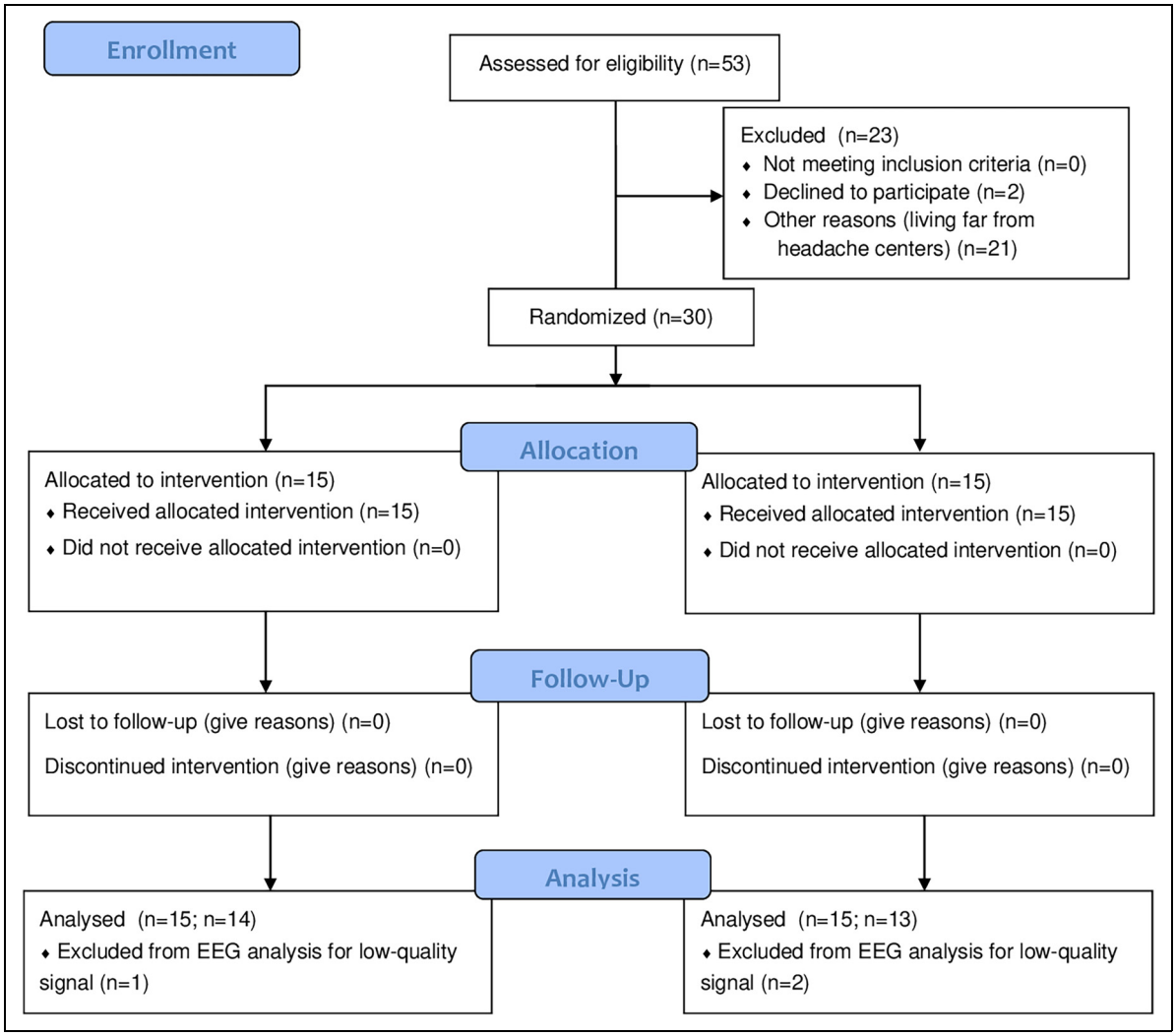

Figure 2. CONSORT flowchart of participants' inclusion. EEG, electroencephalogram.

Table 1. Characteristics of participants at screening (i.e., before starting treatment with monoclonal antibodies) and at baseline (i.e., during the 28 days before transcranial direct current stimulation). Results of comparisons between groups and corresponding effect size are also reported.

	Active (n = 15)	Sham (n = 15)	Statistic†	Effect size†	*p*-value
Female, n (%)	12 (80.0%)	12 (80.0%)	0.000	0.000	>0.999
Age, mean ± SD	45.0 ± 10.5	49.1 ± 12.2	−0.978	−0.357	0.337
Screening					
Years of migraine history, mean ± SD	27.3 ± 11.7	31.9 ± 15.7	−0.911	0.333	0.371
Chronic migraine, n (%)	11 (73.3)	13 (86.7)	0.208	0.167	0.648
Aura, n (%)	2 (13.3)	6 (40.0)	1.534	0.464	0.216
Medication overuse, n (%)	11 (73.3)	9 (64.3)	0.276	0.193	0.599
Headache days/28 days*, mean ± SD	16.5 ± 9.1	16.5 ± 9.4	0.104	0.038	0.918
Migraine days/28 days*, mean ± SD	14.4 ± 8.6	15.3 ± 9.1	−0.278	−0.102	0.783
Acute medications/28 days*, mean ± SD	14.9 ± 13.3	13.7 ± 10.7	0.272	0.099	0.788
Baseline					
Headache days /28 days, mean ± SD	11.2 ± 10.7	15.6 ± 10.6	−1.039	−0.379	0.310
Migraine days/28 days, mean ± SD	13.2 ± 6.2	16.9 ± 7.7	−1.408	−0.514	0.171
Acute medications/28 days, mean ± SD	12.9 ± 5.9	16.6 ± 13.0	−0.975	−0.356	0.343
mMIDAS score, mean ± SD	15.5 ± 11.8	17.1 ± 23.4	−0.236	−0.086	0.816
HIT-6 score, mean ± SD	62.9 ± 7.2	60.7 ± 7.4	0.804	−0.294	0.428
ASC-12 score, mean ± SD	1.2 ± 1.6	3.5 ± 4.0	−1.945	−0.710	0.070
HADS-A score, mean ± SD	6.1 ± 3.9	5.5 ± 4.2	0.407	0.148	0.687
HADS-D score, mean ± SD	6.3 ± 4.5	4.7 ± 4.0	1.079	0.394	0.290
PSQI score, mean ± SD	6.3 ± 2.7	6.3 ± 4.0	0.000	0.000	>0.999

*Data on the 90 days before starting treatment with monoclonal antibodies, normalized to a 4-week period.
†For continuous variables, statistical parameters were derived from independent t-test (statistic: *t*-value, effect size: Cohen's *d*). For categorical variables, statistical parameters were obtained from chi-squared test (statistic: χ^2, effect size: φ coefficient). ASC-12 = Allodynia Symptom Checklist; HADS-A = Hospital Anxiety and Depression Scale – Anxiety; HADS-D = Hospital Anxiety and Depression Scale – Depression; HIT-6 = Headache Impact Test; mMIDAS = monthly Migraine Impact and Disability Assessment Scale; PSQI = Pittsburgh Sleep Quality Index.

(40.0%) were on treatment with erenumab, 10 (33.3%) with galcanezumab and eight (26.7%) with fremanezumab during the study period. Participants' blinding was maintained throughout the study. Twenty-four participants answered the question whether they received active or sham tDCS, while the remaining participants answered that they could not tell. Among the 11 participants treated with active tDCS and answering to the question, only six identified their treatment arm correctly, compared to six of the 13 participants treated with sham tDCS and answering to the question (chi-squared test: $p > 0.999$).

Efficacy endpoints

Referring to the primary efficacy endpoint, ANCOVA indicated that participants treated with active tDCS reported a similar number of headache days at the follow-up assessment compared to those treated with sham tDCS (Table 2).

Referring to secondary endpoints, analyses showed a large effect of tDCS on migraine frequency. Specifically, participants treated with active tDCS reported a lower number of migraine days during the 28 follow-up days compared to those treated with sham tDCS ($p = 0.008$ e $\eta p2 = 0.241$) (Figure 3 and Table 2). A paired *t*-test comparing baseline and follow-up migraine days indicated that the active tDCS group reported a reduction in migraine days during the follow-up period ($t = 2.557$, $p = 0.023$, Cohen's $d = 0.660$). No differences between baseline and follow-up periods emerged within the sham tDCS group ($t = 0.344$, $p = 0.737$, Cohen's $d = 0.092$).

Other efficacy endpoints were not different between active and sham groups (Table 2).

Neurophysiological endpoints

Data from three patients (Active, n = 1; Sham, n = 2) were excluded from the statistical analysis on EEG spectral power due to the poor quality of the signals in one of the recordings. Preliminary between groups comparisons on the EEG spectral powers at baseline showed no significant difference (all uncorrected $p \geq 0.2488$), confirming the comparability of the neurophysiological background in the two groups before the tDCS intervention.

The results of the ANCOVA showed that active tDCS compared to sham led to a significant lower delta power over the frontal regions (Figure 4(b)), on a cluster of channels (AF3: $p = 0.032$, AF4: $p = 0.009$, F1: $p = 0.008$, F2: $p = 0.023$, F3: $p = 0.018$, F4: $p = 0.034$, Fz: $p = 0.011$) that reflects the position of the anodal tDCS electrodes, and over Pz ($p = 0.031$) and P4 ($p = 0.033$). EEG power

Table 2. Efficacy endpoint measures during follow-up. Statistical parameters (*F*, *p* and ηp2) refer to the analyses of covariance with baseline values as covariate.

	Active (n = 15)	Sham (n = 15)	*F*-value	***p***-value	η_p^2
Headache days/28 days, mean ± SD (*primary*)	10.7 ± 10.4	14.9 ± 9.6	0.35	0.560	0.017
Migraine days/28 days, mean ± SD	9.2 ± 3.7	16.6 ± 7.4	8.26	0.008	0.241
Acute medications/28 days, mean ± SD	10.8 ± 6.5	15.3 ± 10.3	3.16	0.087	0.108
mMIDAS score, mean ± SD	16.4 ± 15.2	15.2 ± 13.5	0.32	0.580	0.011
HIT-6 score, mean ± SD	58.5 ± 7.7	56.3 ± 7.3	0.09	0.761	0.003
ASC-12 score, mean ± SD	2.0 ± 1.1	2.6 ± 1.2	0.05	0.822	0.002
HADS-A score, mean ± SD	8.2 ± 3.8	7.4 ± 3.8	0.16	0.691	0.006
HADS-D score, mean ± SD	4.6 ± 3.8	3.5 ± 3.8	0.02	0.878	0.001
PSQI score, mean ± SD	6.5 ± 2.4	6.1 ± 3.2	0.21	0.649	0.008

ASC-12 = Allodynia Symptom Checklist; HADS-A, Hospital Anxiety and Depression Scale – Anxiety; HADS-D = Hospital Anxiety and Depression Scale – Depression; HIT-6 = Headache Impact Test; mMIDAS = monthly Migraine Impact and Disability Assessment Scale; PSQI = Pittsburgh Sleep Quality Index.

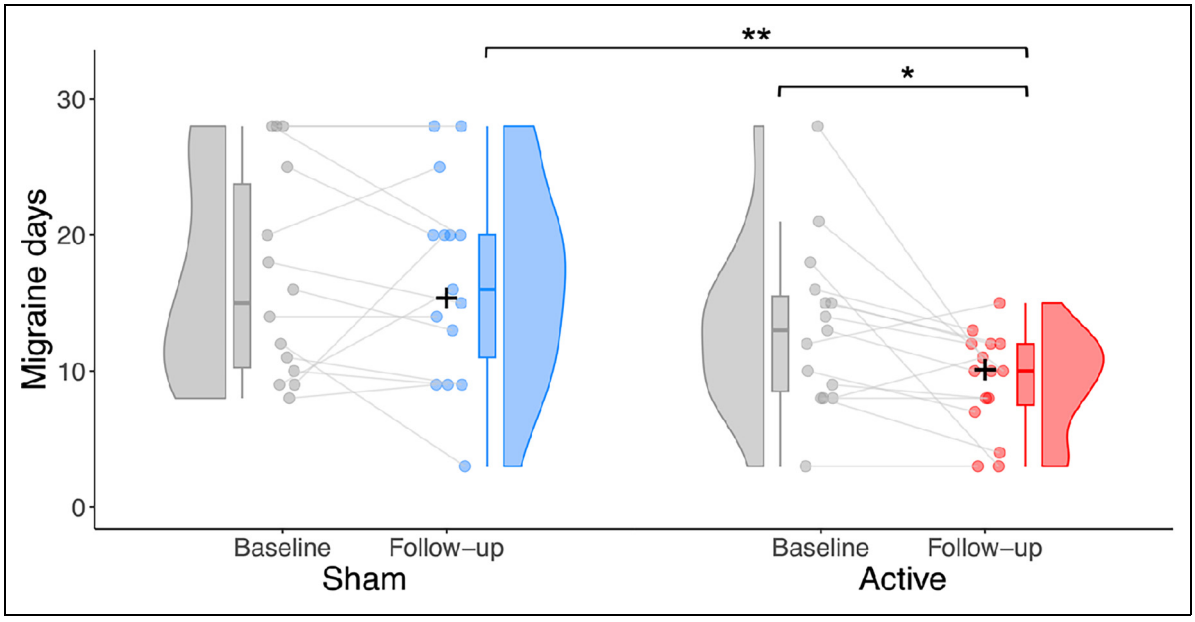

Figure 3. Migraine days during the 28-day baseline and follow-up periods in the active and sham transcranial direct current stimulation (tDCS) groups. Graph combines a density plot, a box plot, and a jitter plot for each group and assessment. Plus symbols represent estimated marginal mean values from the analaysis of covariance (ANCOVA); one asterisk indicates significant differences from paired t-test (*$p = 0.023$), while two asterisks represent significant effect from ANCOVA (**$p = 0.008$).

in the other frequency bands did not significantly differ between groups. No significant correlation was found between migraine days and EEG power in the active tDCS group.

Finally, the exploratory comparisons between EEG spectral power at baseline and at the follow-up within the two groups showed that the main effects of the active tDCS involved a widespread decrease in delta power at frontal regions (Figure 4(c)), as expected from the between groups comparisons. The reduction in low frequency activity was also associated with a significant decrease in beta power on posterior areas (Figure 5(b)), not highlighted by the comparison with sham group but consistent with the placement of the cathodal electrodes, spreading laterally on temporal regions. As expected, sham stimulation had no significant effect on EEG regardless of the frequency band considered ($p > 0.05$).

Safety endpoints

During the stimulation, adverse events were reported by 10 participants in the active group and by seven participants in the sham group. All adverse events were mild and occurred only during the 5-day stimulation period, without any

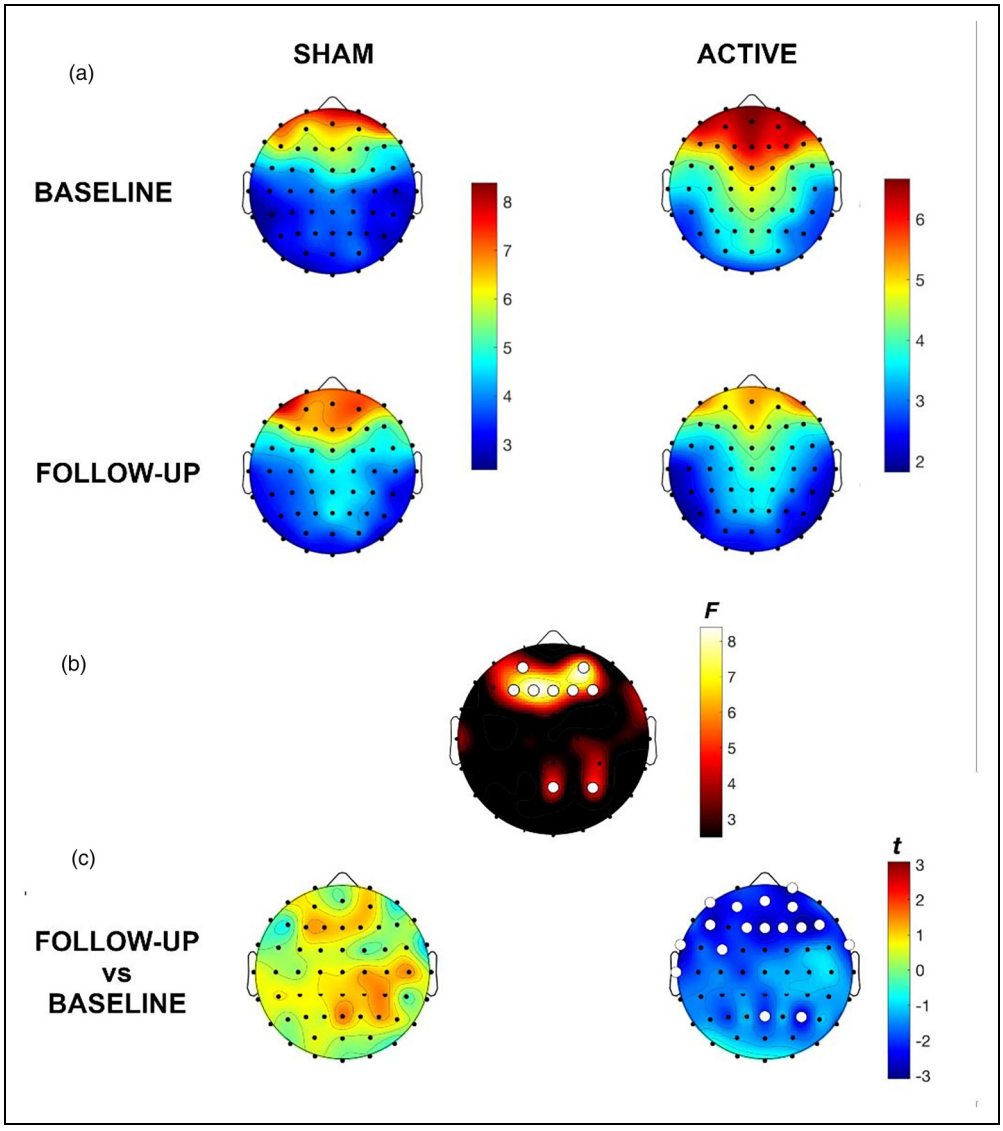

Figure 4. Transcranial direct current stimulation (tDCS) effect on electroencephalographic spectral power. (a) Mean spectral power in the delta band (1–4.5 Hz) at baseline (first row) and follow-up (second row) in the group of patients receiving sham (left column) or active tDCS (right column) as treatment; color scale was set on the minimum and maximum in power values within baseline and follow-up sessions, separately for each group. (b) Topographic distribution of the *F*-values for the factor Group (Active vs. Sham) from the analaysis of covariance on the delta power at follow-up covarying for the power at baseline; white dots indicate channels reporting significant difference according to the false discovery rate (FDR). (c) Topographical distribution of *t*-values from the follow-up vs. baseline comparisons on delta power in the two groups; color scale was set symmetrically on the absolute maximum in the two groups to allow the comparability of the results; white dots indicate channels reporting significant within-group differences according to the FDR correction.

adverse events reported during the follow-up period. Analyses indicated no association between treatment and adverse events (Table 3).

Discussion

Our randomized controlled trial suggests that tDCS is a promising adjunctive treatment to anti-CGRP/R mAbs for migraine prevention and that this combination strategy may represent a tool to further improve the outcomes in migraine prevention. Although the study did not meet its primary efficacy endpoint, active tDCS led to a substantial decrease in migraine days compared to the sham procedure. These results have implications for migraine prevention, the advancement of neuromodulation techniques, and the study of migraine pathophysiology.

Anti-CGRP/R mAbs have demonstrated good efficacy and excellent tolerability for migraine prevention (33,34). However, a proportion of individuals reports significant benefits but a substantial residual migraine burden (18).

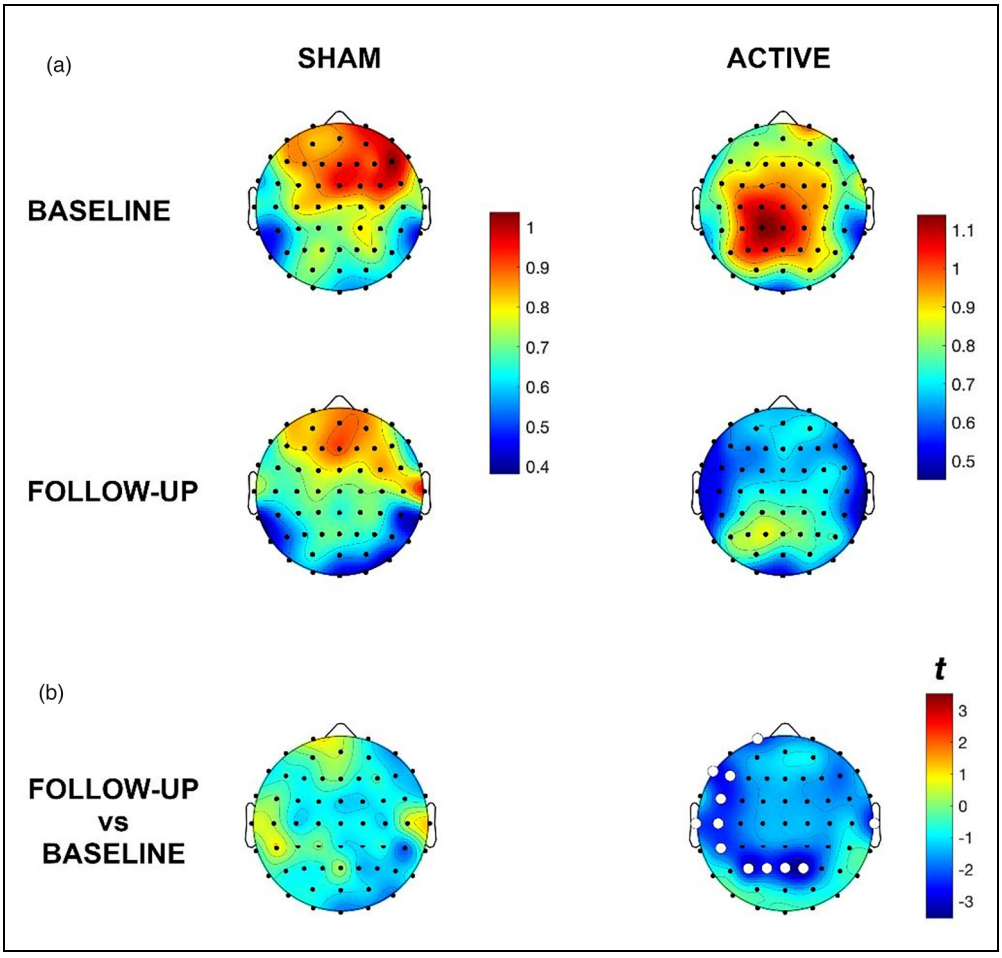

Figure 5. Other changes in brain physiology after transcranial direct current stimulation (tDCS). (a) Mean spectral power in the beta band (13–25.5 Hz) at baseline (first row) and follow-up (second row) in the group of patients receiving sham (left column) or active tDCS (right column) as treatment; color scale was set on the minimum and maximum in power values within baseline and follow-up sessions, separately for each group. (b) Topographical distribution of *t*-values from the follow-up vs. baseline comparisons on beta power in the two groups; color scale was set symmetrically on the absolute maximum in the two groups to allow the comparability of the results; white dots indicate channels reporting significant within-group differences according to the false discovery rate correction.

Table 3. Adverse events (n (%)) during the 5-day stimulation.

	Active (n = 15)	Sham (n = 15)	χ^2	*p*-value	φ
Local paresthesia, n (%)	7 (46.7)	3 (20.0)	1.350	0.245	0.217
Local pain, n (%)	1 (6.7)	–	–	–	–
Burning sensation, n (%)	4 (26.7)	2 (13.3)	0.208	0.648	0.084
Local heating, n (%)	3 (20.0)	2 (13.3)	0.000	>0.999	0.000
Itching, n (%)	8 (53.3)	6 (40.0)	0.134	0.714	0.067
Iron taste	–	1 (6.7)	–	–	–
Fatigue, n (%)	2 (13.3)	–	–	–	–
Other, n (%)	–	1 (6.7)	–	–	–
Any	10 (66.7)	7 (46.7)	0.543	0.461	0.136

Neuromodulation has demonstrated some efficacy in migraine prevention although with high heterogeneity of techniques and study designs (21,35,36,–37). Combination therapy is a viable option for individuals with a measurable but unsatisfactory response to anti-CGRP/R mAbs, given that both treatment approaches possess a high tolerability and they have different targets. To date, however, the combination of the two treatments was not explored yet. In our study, we demonstrated a substantial effect of tDCS on migraine days, while the overall effect on headache days was not significant. A possible explanation for this effect, which will need confirmation in further studies, is that tDCS was able to decrease migraine-related symptoms and possibly headache intensity, therefore decreasing full-blown migraine attacks at the same time as having a less substantial effect on mild, tension type-like headache episodes. The lack of difference between the active and sham groups in other secondary endpoints such as acute medication or patient-reported endpoints might be explained by either the same

migraine-specific effect of tDCS (not acting on the overall burden of headache) or by a lack of statistical power.

As far as we know, anti-CGRP/R mAbs exert their action primarily outside the brain, as they do not cross the blood–brain barrier (16). Their effect on higher-level brain structures controlling pain perception and processing cannot be excluded; however, it is likely indirect and may take time to manifest after initiating an effective treatment. Therefore, neuromodulation techniques that directly act on cortical brain structures are interesting candidates for combination therapy with anti-CGRP/R mAbs . However, even the target of neuromodulation might be wider than the sole brain cortex. The approach of combining anti-CGRP treatments with neuromodulation might provide insights into the mechanisms of migraine generation and prevention in future studies on larger samples compared to the present one.

Various neuromodulation techniques have been used for migraine prevention beside tDCS, including transcranial magnetic stimulation, trigeminal stimulation, and remote electrical neuromodulation (35,37). Compared to other techniques, tDCS involves the stimulation of large cortical areas, allowing for broad modulation of brain activity. In migraine research, commonly used tDCS protocols include anodal (excitatory) stimulation of frontal areas, which is thought to modulate thalamocortical circuits (38,39), and cathodal (inhibitory) stimulation of occipital areas (40,41,42,–43), which are implicated in cortical spreading depolarization phenomena associated with migraine aura (4,44).

To date, there is no agreement on the optimal tDCS protocol for migraine prevention (36). In this trial, we designed a bilateral stimulation protocol combining anodal frontal and cathodal occipital stimulation to target multiple areas relevant to migraine prevention. Our positive results support the efficacy of this tDCS protocol. Notably, the effect on monthly migraine days was greater than the effect on overall headache days and patient-reported endpoints, suggesting a migraine-specific effect.

To assess the neurophysiological effects of tDCS, we employed high-density EEG. This technique can measure short-term changes in cortical electrical activity with high spatial resolution. Our tDCS protocol led to a reduction in slow-frequency cortical activity in frontal areas, likely linked to increased cortical excitability induced by anterior anodal stimulation. Conversely, cathodal stimulation of occipital regions may have reduced cortical excitability in posterior regions, as suggested by the decrease in high-frequency activity observed at follow-up in the active tDCS group. The tDCS montages and schedules used to date for migraine prevention are heterogeneous and mostly non-specific, and it is difficult to judge which are the best parameters for this clinical indication (36). In our study, the protocol was selected to stimulate circuits involved in pain, while its duration was chosen to ensure feasibility and high patient compliance.

Our novel stimulation montage, combining bilateral frontal anodal stimulation with bilateral occipital cathodal stimulation, may have altered the overall balance of cortical excitability by reducing it in posterior regions and increasing it in anterior areas. The anterior component could help to counteract EEG slowing, which has been linked to migraine in EEG studies (45), while the posterior inhibitory component could restabilize the excessive cortical responsiveness of occipital regions observed in individuals with migraine (46). However, despite the effect of our stimulation protocol on the brain cortical activity, our analyses did not reveal a significant correlation between the neurophysiological effect of tDCS and the clinical endpoints. This negative finding could be attributed to the small sample size, which was powered to detect clinical endpoints, while might have been underpowered for EEG data which present a large within- and between-subject variability. This limits the possible insights into how brain activity changes translate into clinical benefits. Future studies should replicate both the EEG and clinical effects of our stimulation protocol in a larger sample to investigate this relationship with adequate statistical power.

It is noteworthy that, in the present study, participants on stable treatment wih anti-CGRP/R mAbs exhibited changes in cortical activity and improvement in migraine symptoms following tDCS treatment. This finding further reinforces the idea that anti-CGRP/R mAbs primarily act outside the brain and that neuromodulation can exert a synergistic effect. However, it should be noted that participants in our trial were selected based on a poor response to anti-CGRP/R mAbs, suggesting that their migraine attacks depended only partially on CGRP release.

This study has several strengths, including its design and the use of a tDCS protocol specifically designed for migraine prevention, simple and feasible in routine clinical settings. However, we acknowledge some limitations, including the short duration of the tDCS treatment (5 days) and of the follow-up period (28 days) that might have led to underestimating the true efficacy and persistence of the clinical effect. Additionally, we cannot exclude a selection bias associated with the enrollment of participants. Participants were selected from individuals living near the study centers or those with flexible schedules, potentially introducing selection bias. This limitation could affect the representativeness of the study population and the applicability of results to broader migraine populations. Although some participants had conditions such as medication overuse headache, chronic migraine or menstrually related migraine, we were unable to perform any subgroup analyses because the study is underpowered to detect subgroup differences. Studies have also suggested possibile gender differences on the benefits from CGRP targeting treatments (47); we were unable to test possible gender differences of the proposed strategy. Therefore, our study cannot provide insights on which subpopulation of patients with migraine is best suited for tDCS. Limited

study power may also have led to an oversight of potential subtle clinical or neurophysiological effects of tDCS.

Conclusions

Our multicenter, randomized, double-blind, sham-controlled trial suggests that a specifically designed tDCS protocol was effective as an adjunctive treatment to anti-CGRP/R mAbs to maximize benefits of migraine prevention. Our results underscore the potential of combination treatments and highlight the need for further clinical trials (36) aiming to optimize treatment strategies for individuals with refractory migraine.

Clinical implications

- tDCS as an adjunct: tDCS, applied alongside CGRP monoclonal antibodies, resulted in a significant reduction in migraine days during the 28-day follow-up compared to the sham group.
- Neurophysiological effects: active tDCS induced a significant decrease in delta power in frontal regions, suggesting an impact on central migraine mechanisms.
- Reduction in migraine days: participants receiving active tDCS reported fewer migraine days during the 28-day follow-up compared to the sham group.
- Safety profile: tDCS was well tolerated, with no serious adverse events reported.
- Potential for combination therapy: the results support the potential of combining peripheral and central approaches to enhance response in patients who are refractory to CGRP monoclonal antibodies.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Ethical statement

The study was approved by the Ethics Committee for the districts of L'Aquila and Teramo with Protocol Number 272/21. All patients provided their written informed consent to participate in the study

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