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Monoclonal antibody against CGRP (TEV-48125) for preventive treatment of episodic cluster headache: a phase II randomized clinical trial protocol

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Abstract:

Background: *Episodic Cluster Headache (CH) is the most prevalent and peculiar form of trigeminal autonomic cephalalgias. It is also considered the most severe among primary headache syndromes with a relevant destructive impact on quality of life, which makes it a highly disabling disorder. Despite availability of adequate options for acute attacks, at the present time there is no ideal effective preventive treatment for this condition. Preliminary evidence on treatment efficacy and safety of monoclonal antibodies against Calcitonin Gene-Related Peptide or its receptor has shown promising results as novel therapies for this type of disorder. The aim of this study is to analyze the effectiveness of the anti-CGRP antibody TEV-48125 against placebo, as a preventive strategy for episodic cluster headache on reducing the frequency of headache attacks during a headache episode.*

Methods: *This study is a randomized, single-center, placebo controlled, triple-blind, parallel group trial with 1:1 allocation of 60 patients newly diagnosed with episodic CH to receive after an 8-week baseline observation phase either monoclonal anti-CGRP antibody TEV-48125 or placebo at weeks 1 and 5 over the course of 8 weeks during the experimental phase. Frequency of attacks will be assessed per week for 8 weeks during the baseline observation phase and the experimental phase. Primary endpoint is the reduction in frequency of headache attacks from baseline during a cluster headache episode compared to placebo.*

Discussion*: This trial is a triple-blinded randomized placebo-controlled trial for a rare disease where preventive treatment is urgently needed. Potential limitations and challenges are the triple-blind approach and patient adherence but will be handled to keep the impact at minimum.*

Keywords: *Cluster headache, anti-CGRP antibody, TEV-48125, Calcitonine Gene-Related Peptide, preventive treatment, headache.*

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INTRODUCTION

Cluster headache (CH) is the most prevalent among the trigeminal autonomic cephalalgias and has an overall prevalence among the general population of 53 people per 100,000 with a male/female ratio of 4:1 (Fischera, Marziniak, Gralow, & Evers, 2008). The pain associated with this type of headache is usually unilateral, periorbital and has accompanying ipsilateral autonomic symptoms (Weatherall et al., 2005).

In almost 85% of CH patients, cluster headache presents episodically. Episodes typically occur with a circannual rhythm and an average duration of 6 to 8 weeks, although duration can range from 1 week and up to 12 months. The average number of cluster periods consists of at least 2 per year. During a cluster episode CH patient experience headache attacks, with an average number of 14 attacks per week is and an average duration per attack of 15 to 180 minutes (Weatherall et al., 2005; Jensen & Stovner, 2008).

CH has three cardinal features: severe unilateral pain with a distribution along the first division of the trigeminal nerve, characteristic autonomic features and stereotypical presentation (May & Schulte, 2016). The symptoms typically associated with the cluster headache pain are ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis and/or eyelid edema, and/or with restlessness or agitation (Headache Classification Committee of the International Headache Society, 2013). Cluster headache pain is considered one of the most severe pain syndromes. Female patients who suffer from CH attacks describe the pain as 'worse than childbirth' (Halker, Vargas, & Dodick, 2010), and its intensity is estimated to be 100 to 1000 times worse than migraine (Rozen, 2010).

The exact neurophysiological pathways of CH are currently poorly understood but one of the most accepted theories states that attacks start by hypothalamic activation with secondary activation of the trigeminal-autonomic reflex. Pain also seems to be at least partially mediated by increased Calcitonin Gene-Related Peptide (CGRP) plasma levels (Hansen, Hauge, Olesen, & Ashina, 2010). This potent vasodilator neuropeptide is released by the activated trigeminal system and plays an important role in pain signaling neurotransmission (May & Schulte, 2016). Recently the G-allele of the G1246A hypocretin receptor 2 gene (HCRTR2) polymorphism has been found significantly associated with CH, suggesting that the hypocretin/orexin system may be also involved with CH pain transmission and observed autonomic symptoms (Rainero et al., 2007).

For many years, inhaled oxygen and triptans have been used therapeutically in acute attacks during a CH episode (Cohen, Burns, & Goadsby, 2009; Law, Derry, & Moore, 2013). Although adequate treatment for acute attacks exists, no effective preventive regimen is currently available. Verapamil has been one of the prophylactic treatment cornerstones; however, there is lack of evidence supporting effectiveness of verapamil or other drugs in this context. Moreover, current therapeutic options are not free of adverse effects and may have potential interactions with various medications. The absence of a specific and effective preventive treatment for this severely intense and frequently recurring type of headache contributes to its nature of a highly disabling disorder.

In addition to the significant impact this condition has on daily routines and quality of life, it has also an important economic repercussion. This occurs both in an individual level due to treatment costs, and in a public health spectrum due to recurring absenteeism at work and lesser productivity by patients (Gaul et al., 2011). Finding an appropriate target for preventive treatment to reduce pain intensity and frequency of attacks is therefore important to improve patients' quality of life as well as to reduce the overall disabling impact and economic burden of this disease (Global Burden of Disease Study 2013 Collaborators, 2015; Stewart, Ricci, Chee, Morganstein, & Lipton, 2003).

During the past decade, the CGRP peptides have become a primary target for drug development to treat migraine and also trigeminal headaches including CH (Ho, Edvinsson, & Goadsby, 2010). Preliminary evidence on treatment efficacy and safety of monoclonal antibodies against CGRP or their receptor have been reassuring of their use as a therapeutic target for this type of disorders (Bigal et al., 2013). The recombinant humanized anti-CGRP antibody TEV-48125 has shown a safe profile in preclinical and Phase 1 studies (Bigal et al., 2013). Recently, preliminary efficacy in the treatment of migraine has been demonstrated in a Phase 2b trial (Bigal et al., 2015a). This is consistent with results of Phase 2 trials of other monoclonal antibodies against CGRP (LY2951742, ALD403) and the CGRP receptor (AMG334) that have shown those antibodies to be promising options for novel pharmacologic treatments of migraine headache (Sun et al., 2016). One Phase 2 trial using ALD403 anti-CGRP antibody has also shown efficacy in CH (Bigal et al., 2015b). Besides promising efficacy, all of these Phase 2 trials have also demonstrated very low rates of adverse events. The four humanized monoclonal antibodies previously mentioned are currently in phase 3 trials for migraine, and ALD403 in phase 3 trials for CH treatment.

As a result, the aim of this phase 2 randomized placebo controlled clinical trial protocol is to study the safety and effectiveness of the anti-CGRP antibody TEV-48125 against placebo as a preventive strategy for episodic cluster headache. Our hypothesis is that the anti-CGRP antibody TEV-48125 is effective as a preventive strategy of episodic cluster headache by reducing the frequency of headache attacks during a headache episode as compared to placebo.

MATERIALS AND METHODS

Study Design

The suggested protocol is a randomized, single-center, placebo controlled, triple-blind, parallel group trial with 1:1 allocation to receive either monoclonal anti-CGRP antibody TEV-48125 subcutaneous injection in the abdominal wall (900 mg/dose) or placebo injection (figure 1). Participants will be recruited after the first

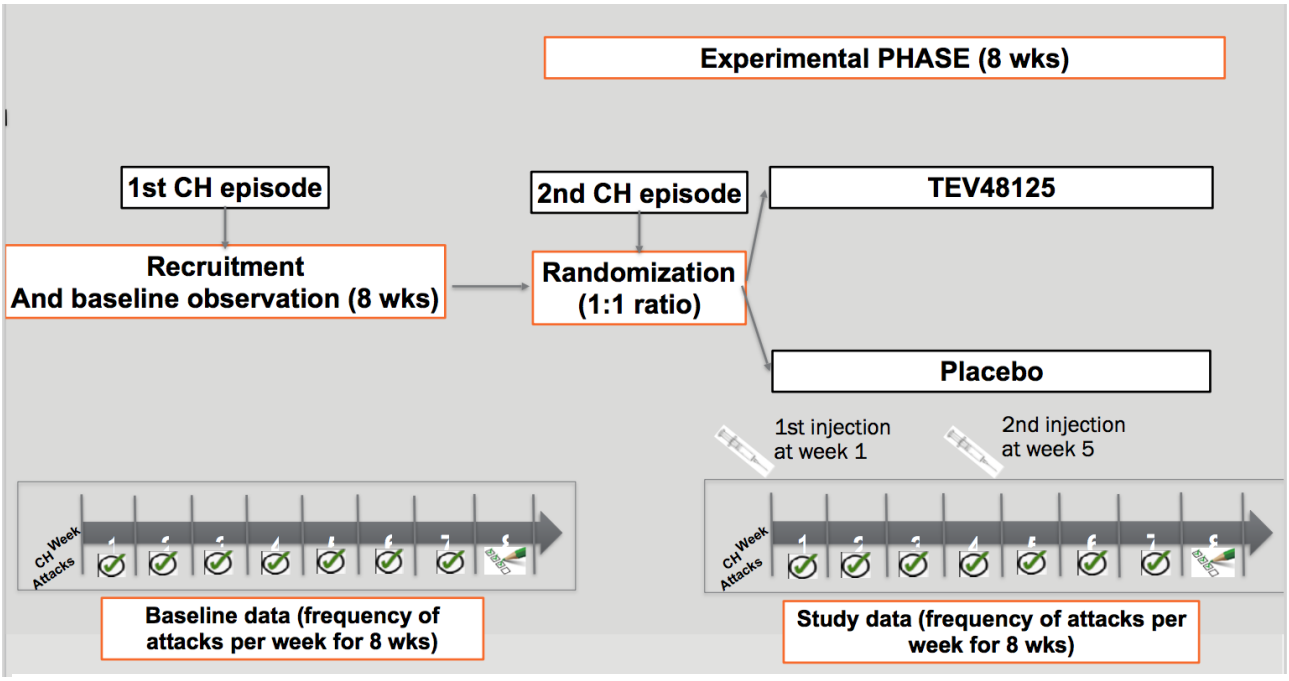

Figure1. Study Protocol Design

diagnosed CH episode and will be followed without receiving any intervention for the maximum period of 8 weeks. After the onset of the second CH episode during this period, patients will be randomized to receive either TEV-48125 or placebo at weeks 1 and 5. Follow-up will extend until week 8 after randomization. Study data will be collected and managed using RedCAP, an electronic data capture tool. Approval from the investigational review board (IRB) will be obtained and conduct will conform to the principles of the Declaration of Helsinki of the World Medical Association.

Intervention

The intervention being studied is the subcutaneous injection of a 900 mg dose of anti-CGRP antibody TEV-48125 (group A) or placebo injection (group B) subcutaneously in the abdominal wall during the first and the 5th week of the second cluster episode.

Endpoints

The primary outcome is the mean change from baseline in number of CH attacks during the 8th week or the last week of the episode.

Secondary outcomes to be analyzed are mean change from baseline in the average weekly frequency of CH attacks from the first to the 8th week (questionnaire), change from baseline in the duration of cluster cycles (mean proportion of change), change in average weekly intensity of CH attacks by a Visual Analogic Scale (Torelli & Manzoni, 2003), percentage of participants developing anti-drug antibodies to TEV-48125 (baseline through 8th week), pharmacokinetics including serum concentration of TEV-48125 (at 2th, 4th, 6th and 8th weeks) and safety.

Eligibility Criteria

The study population consists of adult individuals from 18 to 65 years of age, who have been diagnosed with episodic cluster headache. The exclusion criteria comprise the presence of immune disease, use of immunosuppressant or immunomodulating agents, contraindication for subcutaneous injections, pregnancy or breastfeeding. In addition, patients with the following co-morbidities will also be excluded from the trial: HIV positive, cancer, bleeding conditions, liver or kidney disease, and diabetes. Enrollment in any other research study also excludes individuals from this study.

Recruitment Strategy

Our study population is composed of tertiary hospital inpatients or outpatients with diagnosis of cluster headache who were referred from pain management units and neurology departments of tertiary centers from Sao Paulo (Brazil), during an interval of two years.

Medical records are to be reviewed to identify patients who meet the eligibility criteria. Candidates will be approached by direct invitation to participate in our study, through a personal or group interview, and will be informed about purpose, objectives, features, benefits and potential risks related to the clinical trial. All participants must provide written informed consent.

Adherence

Participants will receive training about the study and what it involves before starting any intervention. Reminder sessions will take place at weekly visits and a trained nurse will periodically contact participants.

In order to ensure proper adherence and reduce attrition, patients will be allowed to take rescue medications (triptans, inhaled oxygen) during cluster attacks, as prescribed by the patient's physician.

Randomization

All patients enrolled are to be allocated to one of the two study groups with allocation concealment (TEV-48125 = group A, placebo = group B) based on a computer-generated randomization plan provided by the study coordinator. This plan includes the number of the patient enrolled (1-60) and a corresponding letter A or B. The plan features a block randomization with variable block sizes of 4-6, stratified by gender.

Blinding

The trial features a triple-blind design with, firstly, blinding of patients; secondly, blinding of enrolling and treating physicians, including the study coordinator; and lastly, blinding of data analysts.

To maintain allocation concealment and blinding during the study, injections will be prepared by the supplying pharmacy. TEV-48125 and placebo injections will be the same in their appearance (volume, size, color). The head of the pharmacy determines study drug allocation and will be the only person knowing the identity of the injections. This information is kept secret from the study coordinator, physicians and researchers involved until the end of the trial, so as to maintain allocation concealment and blinding. The pharmacy is providing TEV-48125 or placebo for the respective study group according to this decision.

To test the effectiveness of blinding, patients are asked whether they believe they had been in the TEV-48125 or placebo group after they have completed the trial.

Emergency Unblinding

Unblinding is permissible at any time when the patient's health is at risk and unblinding may help in patient care. In case of the occurrence of any severe adverse event, unblinding will occur and the event will be reported within 24 hours to the IRB. If this takes place, a 24-hour emergency phone service provided by the head of pharmacy can reveal the patients allocated intervention immediately.

Unblinding should not necessarily be a reason for study drug discontinuation. The need for discontinuation will be decided on each particular case by the study coordinator.

Sample Size Calculation

We calculated that a sample of 60 patients (30 patients per arm) will be required in order to detect a 20% reduction in the primary outcome of mean change from baseline in number of CH attacks, from 20% reduction in the placebo group (14 to 11.2 attacks per week) to 4% reduction in the intervention arm (14 to 8.4 attacks per week), with 90% power and a two-sided type I error of 0.05, accounting for a 15% dropout rate.

Statistical Analysis Plan

All statistical analysis will be performed using the statistical software STATA 14 (StataCorp LP, College Station, Texas, USA).

The primary outcome (mean change from baseline in number of CH attacks during the 8th week or the last week of the episode) will be compared with an unpaired t-test. Secondary analysis for this endpoint will consist of a multiple regression analysis adjusting for covariates such as age, BMI, race, gender, duration of episodes and number of episodes.

Secondary outcomes will be tested with an unpaired t-test for each of the mean changes from baseline in the average weekly frequency of CH attacks from the first to the 8th week, change from baseline in the duration of cluster cycles and change in average weekly intensity of CH attacks. The proportion of participants developing anti-drug antibodies to TEV-48125 will be compared with a chi-squared test for independence. Intention-to-Treat (ITT) analysis will be used. Missing data will be imputed using a multiple imputation approach.

Data Management

An electronic case report form (CRF) will be filled out for each participant. Data will then be uploaded in a HIPAA-compliant electronic research data management system (RedCAP). In addition, patients will fill out and report weekly questionnaires.

In order to promote data quality, uploaded data will be validated weekly. A coding system for adverse events and for medications labels will also be performed to ensure safety. Moreover, so as to further protect participants' confidentiality, data will only be available to the principal investigator and the staff in charge of data validation.

Data Monitoring

A Data Monitoring Committee (DMC) comprised of a neurologist and a general physician will be assembled. This committee will be responsible for checking the accuracy of the data and guaranteeing safety of the participants and protocol adherence by the research group.

IRB submission

The study protocol will be submitted to local Institutional Review Board (IRB) for approval.

Registration

The trial will be registered with www.clinicaltrials.gov.

DISCUSSION

Episodic cluster headache, although not a very common disease, is a disabling condition that highly affects patients' quality of life and can cause great economic burden (Stewart et al., 2003). One of the central reasons for this is the lack of a well-defined preventive maintenance treatment to decrease the number of attacks during CH episodes and to offer good control of the symptoms. Some therapies have demonstrated effectiveness in previous trials (Robbins, Starling, Pringsheim, Becker, & Schwedt, 2016). Nevertheless, these results still differ greatly from what is observed in clinical practice. Finding an effective drug that can decrease the frequency and severity of cluster headache attacks, therefore, could improve patients' quality of life and reducing the economic burden of this disease. Thus, this clinical trial and its results could have major effect in future clinical practice. Confirmation of findings from preliminary studies employing the strategy of blocking the CGRP pathway (Bigal, Walter, & Rapoport, 2015) would have a breakthrough impact on the management of cluster headaches in clinical practice. Likewise, it is anticipated that the guidelines for chronic headaches would be redefined worldwide.

The main strengths of this study are the design using two phases (baseline and experimental phase) and the use of a control (placebo) with allocation concealment and triple-blinding. The fact that patients undergo an initial observation period allows for better measurement of changes in frequency of attacks before and after randomization. It is also a feasible trial given that patients will be recruited from neurological centers, offering enough availability of potential subjects. They will also be followed with weekly visits, which can decrease the rate of dropouts.

Potential limitations of this study include difficulty in maintaining patient adherence, given that cluster attacks could cause patients to abandon treatment, especially the ones randomized to the placebo group. However, this would be partially controlled by providing proper rescue treatment during cluster attacks if needed. Moreover, weekly reminder sessions and follow-up by phone will help reduce lack of adherence for other causes. Another limitation may be related to the triple-blind nature of the study, which, although ideal, may be difficult to maintain in practice. However, all efforts will be made to ensure its success.

Further studies must be conducted to assess the cost-effectiveness of this intervention if proven to be efficacious. The potential is to have an important economic impact by reducing missing work hours and days due to sickness and higher productivity due to better patient work performance in light of having an effective preventive option for the cluster headache.

Therefore, the possibility of better control of this condition might help society change the natural history of this heretofore disabling disease.

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Conflict of interest and financial disclosure

The authors followed the International Committee or Journal of Medical Journals Editors (ICMJE) form for disclosure of potential conflicts of interest. All listed authors concur with the submission of the manuscript, the final version has been approved by all authors. The authors have no financial or personal conflicts of interest.

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