TITLE: A comparison of Rimegepant Orally Disintegrating Tablet (Nurtec ODT) to Rizatriptan Benzoate Orally Disintegrating Tablet (Maxalt MLT-ODT) in Adult Patients presenting to the ED with Migraine Headache: randomized, double-blind, clinical trial

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INTRODUCTION

Current estimates suggest more than 1 million patients visit the Emergency Department (ED) annually for acute migraine attacks (1). Not only are these attacks debilitating, but the management is also complicated by a wide range of analgesic regimens, none of which offer guaranteed relief. At present, the satisfaction with ED treatment of headache is low, and despite the multitude of available medications, the evidence- based treatment options are often quite limited (2-4).

Among people with migraine who have no restrictions on choice of acute treatment, one-third remain dissatisfied with their current treatment. More than 80% of people who are dissatisfied cite slow onset of action, incomplete relief, a return of headache pain within 24 h of an initial response to treatment (i.e., relapse), and side-effects as reasons for dissatisfaction (5). There are over twenty different types of medications available to the ED clinicians for managing headache, many with different routes of administration (parenteral, intranasal, subcutaneous, and oral) (3, 6, and 7). Many of these medications are provided in so-called "headache cocktail", which varies based on the physician, institution, and patient preferences (6, 7). The optimal medication should provide fast, sustained pain relief, while having little to no side effects. However, only one third of patients managed in the ED for headache experience sustained pain relief (8). Furthermore, many of the analgesic options currently used in the ED's cause debilitating side effects such as drowsiness, dizziness, restlessness, akathisia, and dry mouth. (5-7).

Parenteral anti-dopaminergic agents in combination with an NSAID, acetaminophen, and dexamethasone will reduce pain and nausea and are often considered as a first line agents of choice (6, 7). Additionally, subcutaneous sumatriptan is highly efficacious for acute migraine, with a number needed to treat of 2 for headache relief and 3.2 for sustained headache freedom when compared with placebo (9) When compared head-to-head with IV antidopaminergic medications, subcutaneous sumatriptan is generally less efficacious than the antidopaminergic medications, and thus has not been used with much frequency in the ED setting (10,11).

Oral second-generation triptans can play a role for certain patients who can tolerate oral medication and who do not need IV access for hydration. Although not tested specifically in the ED setting, highly effective oral medications can save nursing resources and may improve throughput times (9).

Thus, ED clinicians are in need of an analgesic regimen that is not only quick and efficacious but also contains minimal side effects to return the patient to their baseline quality of life. More recently, Rimegepant (Nurtec), a small molecule calcitonin gene-related peptide receptor antagonist, has shown efficacy in the acute treatment of migraine using a standard tablet formulation (12).

BACKGROUND

Rimegepant (Nurtec ODT)

Rimegepant is an orally administered small molecule CGRP receptor antagonist with efficacy in the acute treatment of migraine. Following oral administration of NURTEC Orally Disintegrating Tablet (ODT), Rimegepant is absorbed with the maximum concentration at 1.5 hours. The absolute oral bioavailability of Rimegepant is approximately 64%. Rimegepant is primarily metabolized by CYP3A4 and to a lesser extent by CYP2C9. Rimegepant is primarily eliminated in unchanged form (~77% of the dose) with no major metabolites (i.e., > 10%) detected in plasma.

The most common adverse reaction is nausea (2% in patients who received NURTEC ODT compared to 0.4% of patients who received placebo). Hypersensitivity, including dyspnea and severe rash, occurred in less than 1% of patients treated with NURTEC ODT.
NURTEC ODT 75 mg orally disintegrating tablets are white to off-white, circular, debossed with the symbol, and supplied in cartons containing a blister pack of 8 orally disintegrating tablets.

In an earlier double-blind, randomized, placebo-controlled, dose-ranging, phase 2b study,13 811 adults with migraine were treated with Rimegepant oral capsules in single doses ranging from 10 mg to 600 mg, sumatriptan 100 mg oral encapsulated tablets, or matching placebo. Dose response was flat and broad, and durable efficacy was shown at multiple doses. The 75 mg dose of Rimegepant was selected for phase 3 trials because it was significantly superior to placebo on the pain-free, nausea-free, photophobia-free, and phonophobia-free endpoints at 2 h, had sustained benefits through 48 h post-dose, and was well tolerated (13).

Two methodologically identical, randomized, double-blind, placebo-controlled phase 3 trials (NCT03235479; NCT03237845) were subsequently done with Rimegepant 75 mg oral tablet. Each trial showed that Rimegepant was significantly more effective than placebo on the coprimary efficacy endpoints of freedom from pain and freedom from the most bothersome symptom associated with migraine at 2 h post-dose, and on key secondary endpoints, including 2 h pain relief.

An orally disintegrating tablet (ODT) of Rimegepant was developed by Biohaven Pharmaceuticals with the intention of optimizing its absorption rate and allowing administration without liquids, which might be of clinical importance to patients with migraine who experience nausea and vomiting. A phase 1 study14 of the ODT formulation administered sublingually showed bioequivalence to and significantly faster absorption than the oral tablet used in previous phase 3 trials. Lastly, in a double-blind, randomized, placebo-controlled, multi-center phase 3 trial that include adults aged 18 years or older with history of migraine of at least 1 year who were randomly assigned to receive Rimegepant (75 mg orally disintegrating tablet) or placebo, Rimegepant orally disintegrating tablet was superior to placebo for freedom from pain (21% *vs* 11%, p<0·0001; risk difference 10, 95% CI 6–14) and freedom from the most bothersome symptom (35% *vs* 27%, p=0·0009; risk difference 8, 95% CI 3–13). The most common adverse events were nausea (14).

Rizatriptan Benzoate (Maxalt MLT-ODT)

MAXALT* contains rizatriptan benzoate, a selective 5-hydroxytryptamine1B/1D (5-HT1B/1D) receptor agonist, Rizatriptan benzoate. Rizatriptan binds with high affinity to human cloned 5-HT1B and 5-HT1D receptors which leads to activation of these receptors results in cranial vessel constriction, inhibition of neuropeptide release and reduced transmission in trigeminal pain pathways with resultant relieve of the headache (15).

Rizatriptan is completely absorbed following oral administration. The mean oral absolute bioavailability of the MAXALT Tablet is about 45% and mean peak plasma concentrations (C max) are reached in approximately 1-1.5 hours (T max). The presence of a migraine headache did not appear to affect the absorption or pharmacokinetics of rizatriptan. Food has no significant effect on the bioavailability of rizatriptan but delays the time to reach peak concentration by an hour. In clinical trials, MAXALT was administered without regard to food. The plasma half-life of rizatriptan in males and females averages 2-3 hours (16).

The efficacy of MAXALT Tablets was established in four multicenter, randomized, placebo-controlled trials. Patients enrolled in these studies were primarily female (84%) and Caucasian (88%), with a mean age of 40 years (range of 18 to 71). Patients were instructed to treat a moderate to severe headache. Headache response, defined as a reduction of moderate or severe headache pain to no or mild headache pain, was assessed for up to 2 hours (Study 1) or up to 4 hours after dosing (Studies 2, 3 and 4). Associated symptoms of nausea, photophobia, and phonophobia and maintenance of response up to 24 hours post-dose were evaluated. A second dose of MAXALT Tablets was allowed 2 to 24 hours after dosing for treatment of recurrent headache in Studies 1 and 2. Additional analgesics and/or antiemetics were allowed 2 hours after initial treatment for rescue in all four studies (17).

The efficacy of MAXALT-MLT was established in two multicenter, randomized, placebo-controlled trials that were similar in design to the trials of MAXALT Tablets In both studies, the percentage of patients achieving headache response 2 hours after treatment was significantly greater in patients who received either MAXALT-MLT 5 or 10 mg compared to those who received placebo. For patients with migraine-associated photophobia and phonophobia at baseline, there was a decreased incidence of these symptoms following administration of MAXALT-MLT as compared to placebo (18).

STUDY OBJECTIVES

To compare analgesic efficacy of orally administered Rimegepant ODT to Rizatriptan ODT for management of acute migraine headache in adult ED patients.

HYPOTHESIS

We hypothesize that the administration of Rimegepant ODT would provide better analgesic efficacy than Rizatriptan ODT with respect to analgesic efficacy at 60 min and 120 minutes in ED patients with acute headache.

STUDY DESIGN

Design

This is a prospective, randomized, double-blind superiority trial evaluating and comparing analgesic efficacy and safety of Rimegepant ODT 75 mg to Rizatriptan ODT 10 mg in adult patients presenting to the ED of Maimonides Medical Center with acute migraine headache.

Setting

We will conduct the study in the emergency department of Maimonides Medical Center, an urban emergency department that receives over 120,000 adult visits annually. The emergency department is staffed on weekdays by salaried, trained, bilingual (English and Spanish) research associates who execute research studies under the supervision of the principal investigators.

Selection of participants

Adult patients between ages of 18 and 65 presenting to the ED with an acute exacerbation of a migraine without aura as defined by the International Classification of Headache Disorders, 3rd edition criteria for migraine without aura or for probable migraine without aura (19), with an initial pain score of 5 or more on a standard 11- point (0 to 10) numeric rating scale (20), and requiring oral analgesia as determined by the treating attending physician will be eligible for participation. Subjects' screening and enrollment will be performed by study investigators and research assistants. All patients will be enrolled at various times of the day when study investigators will be available for patient enrollment and an ED pharmacist will be available for medication preparation.

Eligibility Criteria

Adult patients between ages of 18 and 65 years of age presenting to the ED with acute headache (<7 days) and an initial pain score of 5 on a standard 11- point (0 to 10) numeric rating scale. Patients will have to be awake, alert, and oriented to person, place, and time, and will be able to demonstrate understanding of the informed consent process and content. Patients also will have to demonstrate ability to verbalize the nature of any adverse effects they might experience as well as to express their pain severity by using the NRS.

Exclusion Criteria

- Allergy to Rimegepant or Rizatriptan
- Pregnancy and breastfeeding
- Unstable vital signs
- Inability to provide consent
- Suspicion for disease process other than migraine (those requiring emergent brain imaging, with a temperature of 100.4 °F, with objective neurologic findings, secondary headache (an "organic" headache))
- Ischemic coronary artery disease (angina pectoris, history of myocardial infarction), coronary artery vasospasm (including Prinzmetal's angina)
- History of stroke or transient ischemic attack
- Peripheral vascular disease
- Ischemic bowel disease,
- Uncontrolled hypertension
- Use of another 5-HT1 agonist, ergotamine-containing medications, or ergot-type medications (methylsergide)
- Hemiplegic or basilar migraine

- Concurrent administration or recent discontinuation (within 2 weeks) of a MAO-A inhibitors
- Current use of Rimegepant as a prophylactic
- Severe Nausea and Vomiting
- Severe headache requiring immediate intervention
- Severe hepatic impairment

- If taking any of the following medications (contraindications):
    - Monoaminoxidaze (MAO) inhibitors (isocarboxazid, linezolid, metaxalone, methylene blue, moclobemide, phenelzine, procarbazine, rasagiline, safinamide, selegiline, tranylcypromine)
    - SSRI- Citalopram, Escitalopram, Sertraline
    - Triptans: Sumatriptan, Zolmitriptan, Imigran
    - Almotriptan.
    - Cabergoline.
    - Dihydroergotamine.
    - Dihydroergotamine intranasal
    - Eletriptan
    - Ergoloid mesylates
    - Ergotamine
    - Frovatriptan
    - Duloxetine
    - Cyclobenzaprine
    - Fluoxetine, velafaxine
    - Trazodone
    - Tramadol
    - TCA: nortriptyline (Pamelor), amitriptyline, protriptyline
    - Amphetamines: methamphetamine (Desoxyn), dextroamphetamine (Adderall, Adderall XR), dextroamphetamine (Dexedrine)
    - azole antifungals (ketoconazole, itraconazole)
    - macrolide antibiotics (clarithromycin, erythromycin)
    - rifamycins (such as rifampin, rifabutin)
    - carbamazepine, phenytoin
    - Cardiac Drug: amiodarone (Nexterone, Pacerone), quinidine, ranolazine (Aspruzyo Sprinkle), verapamil (Verelan, Verelan PM)

Randomization and Blinding

The director of research administration will generate a randomization list by using the SPSS 24 block randomization of 10. The research pharmacist will place study drugs into identical medication cups (one containing Rimegepant ODT 75 mg and another one containing

Rizatriptan ODT 10 mg) and will issue them to the research team. The pharmacist will be the only person aware of the subjects' allocations.

Data Collection Procedures

Each patient will be approached by research associates for acquisition of written informed consent and Health Insurance Portability and Accountability Act authorization after being evaluated by the treating emergency physician and determined to meet study eligibility criteria. When English will not be the participant's primary language, a language- appropriate consent form will be used and non-investigator, hospital-employed, trained interpreters or licensed telephone interpreter will assist in acquisition of informed consent. Baseline pain score will be determined with an 11-point numeric rating scale (0 to 10), described to the patient as "no pain" being 0 and "the worst pain imaginable" being 10.

Research associates will ascertain the subject's headache level every 30 minutes after medication administration for up to 120 minutes. If enrolled subjects required more pain medication at or after one hour had elapsed, they will be given additional medication at the discretion of the treating physician.

The research team will be contacting all of research subjects by telephone 24 hours after ED discharge to ascertain headache status, satisfaction with treatment, and presence of adverse events.

All data will be recorded on data collection sheets, including patients' sex, demographics, medical history, and vital signs, and entered into SPSS (version 24.0; IBM Corp) by the research manager. Confirmation of written consent acquisition for all participants, and statistical analyses will be conducted by the institutional biostatistician who will work independently of any data collection.

Measurement Scales

As a primary measure of headache intensity, we utilized a standard, validated, and reproducible 11-point numerical rating scale (NRS). This scale uses patients' responses in assigning their pain a number between 0 and 10, with 0 representing no pain and ten representing the worst pain imaginable. Secondary measurement scales included a standard four-point pain intensity categorical scale, in which patients describe their pain as "severe", "moderate", "mild", or "none" and a four-point functional disability scale, in which patients describe their headache-related disability as severe ("cannot get up from bed or stretcher"), moderate ("great deal of difficulty doing what I usually do and can only do very minor activities"), mild ("little bit of difficulty doing what I usually do"), or none. These scales will be used in accordance of the recommendation by the International Headache Society for use in migraine research (21).

One hour after medication administration, we will ask all of enrolled patients if they needed more medication for pain. Lastly, we will assess enrolled patients' satisfaction (efficacy and tolerability of the study drug) with treatment by asking each of them, 24 hours after enrollment, whether they would want to receive the same medication the next time they visited the ED with an acute migraine.

Outcome measures

The primary outcome for this study will be a comparison of change in numerical rating scale score between baseline and one hour between two investigational arms.
Secondary outcomes will include:
1. A comparative change in pain score between two groups at 120 minutes
2. A frequency of rescue analgesia at 60 and 120 minutes
3. Sustained headache freedom, defined as achieving a level of "none" on the severe, moderate, mild, and none scale within 2 hours of investigational medication administration and maintaining this level continuously for 24 hours without use of rescue medication.
4. Sustained headache relief, defined as change within 2 hours of the patient's description of headache from severe or moderate to either mild or none without use of rescue medication, and maintaining this level of relief continuously for 24 hours.
6. Headache relief in the ED, defined as change within 2 hours of the patient's description of headache from severe or moderate to either mild or none without the use of rescue medication
7. Headache freedom in the ED, defined as achieving a headache level of "none" within 2 hours without use of rescue medication
8. Achieving a normal functional status by two hours
9. The patient's overall assessment of efficacy and tolerability, expressed as a dichotomous response to the question "Do you want to receive the same medication the next time you visit the ER with a migraine?"

Data Analysis

Data analyses will include frequency distributions and independent-sample t-test to assess differences in pain scores at the various intervals. Mixed-model linear regression will be used to compare changes in pain numeric rating scale across time points.

For categorical outcomes (eg, complete resolution of pain), a X^2 or Fisher's exact test will be used to compare outcomes at 60 and 120 minutes. Based on the validation of a verbally administered rating scale of acute pain in the ED and the comparison of verbal and visual pain scales, we will use a primary outcome consisting of a minimal clinically meaningful difference of 2 points between two groups at the 60-minute and 120-minute pain assessment.

The primary outcome is a mean change in NRS score within each group, bounded by unadjusted 95%CIs. The student's t-test for independent sample will be used to compare mean differences in pain scores the arms. We will report all proportions with 95%CI and compare them using a Chi-square test. We will include all patients who receive rescue medication in all analyses.

Sample Size

Assuming the minimum statistically significant difference of 2 points on NRS, with Standard deviation of 3.0, alpha=0.05, and power of 80%, the sample size will require 37 patients per group. To account for potential loss to follow up (discharge from the ED before 120 minutes, about 10%), we will enroll 40 patients in each group.

Adverse Effects

Common Adverse Effects of Rizatriptan include:

- Allergic Reaction (hypersensitivity)
- Chest pain
- Heaviness, tightness, or pressure in the chest and/or neck
- Pounding heartbeat (palpitations)
- Sensation of burning, warmth, heat, numbness, tightness, or tingling
- Trouble breathing
- Burning, crawling, itching, numbness, prickling, "pins and needles", or tingling feelings
- Increased heartbeat
- Irregular heartbeat
- Pain, tightness, or pressure in the neck, jaw, or throat
- Dry mouth
- Hot flashes
- Lack or loss of strength
- Nausea or vomiting
- Sleepiness or unusual drowsiness
- Elevated heart rate and blood pressure

Common Adverse Effects of Nurtec include:

- Allergic reaction
- Nausea
- Stomach Pain/indigestion
- Difficulty breathing
- Shortness of breath
- Swelling of the throat, tongue, mouth, lips, face or eyes
- Hives
- Rash
- Itching

Serious Adverse Effect Reporting

Any serious adverse event, requiring intervention, will be reported to the IRB within 24 hours of discovery by the research staff. Less serious adverse events will be reported within a week of discovery. There are known expected outcomes and side effects to the medications being received and these are the same risks/side effects as the standard of care – these will be reported if they are serious and require intervention.

DSMB

A DSMB will be held to evaluate data once data for 10 subjects (5 per cohort) has been collected.

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