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Doubtful use of placebo following placebo in recent controlled trials of lasmiditan and ubrogepant for the treatment of migraine attacks

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Abstract

Purpose: In four large controlled trials with lasmiditan and ubrogepant placebo was administered in the first step to demonstrate an effect on migraine attack. In the same trials the investigators also asked the question: is a second dose of the drug effective in non-responders to the first dose? In this phase patients who received placebo in the first phase of the trial again after 2 hours received another dose of placebo.

Conclusion: To be ethical, clinical research requires balancing rigorous science with the protection of human subjects; and it is, in our view, questionable whether placebo was used with "scientific rigor" in the second step of these trials, and this design is not recommended.

Keywords

Placebo, ubrogepant, lasmiditan

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Introduction

Migraine patients who treat attacks with either triptans or other anti-migraine drugs often experience non-response; that is, no pain freedom at 2 h. In theory, non-response could be treated with a rescue medication. The effect of triptans as a rescue drug in patients who were treated with a triptan but failed to respond has so far not been shown in randomized trials (RCTs) (1). In contrast, repeated doses of triptans have been shown to be an effective treatment of recurrence of headache in initially successfully treated migraine attacks (2,3).

In four recent RCTs, lasmiditan, a 5-HT_{1F} receptor agonist (two trials), and ubrogepant, a Calcitonin gene-related peptide (CGRP) receptor antagonist (two trials), have been demonstrated to be effective for the treatment of migraine attacks (4–7). Trials of both interventions were large: 3701 patients in the two lasmiditan RCTs (4,5), and 2681 patients in the two ubrogepant RCTs (6,7). The main purpose was to establish dose-response curves for 3 doses of the drugs and all trials were placebo-controlled (4–7). In addition, probably due to the many patients with no pain freedom at 2 h, these trials also addressed a second research question: whether a second dose of the two drugs could be efficacious as rescue medication in non-responders after 2 hours.

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In the following, the design and results of the four RCTs with two such steps will be described. Our main purpose is to discuss, whether it is ethical and scientifically correct to use placebo twice in the same patient during a trial.

Methods and results of RCTs with lasmiditan and ubrogepant

The results of the of the four placebo-controlled RCTs, two with oral lasmiditan (50 mg, 100 mg, and 200 mg) (4,5), and two RCTs with oral ubrogepant (25 mg, 50 mg, and 100 mg) (6,7) are shown in Table 1.

All three doses of both drugs were superior to placebo (Table 1). Based on therapeutic gain (TG, verum minus placebo) for pain-free at 2 h, a dose-response was present for lasmiditan (7%, 12%, 17%) but not for ubrogepant (6%, 7%, 9%), see Table 1.

In the subsequent second step of each trial, patients who were not pain-free at 2 hours or had a recurrence within 24 hours were allowed to take an optional second dose of the allocated study medication, or their own preferred rescue medication. Approximately half of patients who had received placebo as first dose took placebo again as the second (rescue) dose, whereas in patients treated with lasmiditan or ubrogepant as the first dose were randomized either to receive placebo or to repeat the previous first dose of the active drug.

Lasmiditan followed by lasmiditan as rescue drug was not superior to lasmiditan followed by placebo (8), as shown in Table 1. The results for ubrogepant as second dose rescue treatment were only published as an abstract in 2019 (9). Ubrogepant 50 mg plus ubrogepant 50 mg as rescue drug was superior to ubrogepant 50 mg plus placebo, whereas there was no effect of the two other doses (25 mg and 100 mg) of ubrogepant, see Table 1.

Use of placebo twice in the placebo arms of the lasmiditan and ubrogepant RCTs. In total, 606 of 1262 patients in the lasmiditan RCTs and 409 of 912 patients were allocated to placebo in the ubrogepant RCTs and thus likely received placebo twice. Thus 47% (1015/2174) of patients in the 4 RCTs from the original placebo group received another "placebo treatment as rescue medication".

Comments

Use of repeated doses of placebo in the placebo groups of RCTs with lasmiditan and ubrogepant

In the most recent Guidelines of the International Headache Society (IHS) for RCTs from 2019 of acute treatment of migraine in adults (10), it is recommended that: "Interventions under evaluation for the acute treatment of migraine should be compared with placebo". This recommendation is based on two important points: 1) The placebo effect varies widely between placebo-controlled trials, even of the same drugs (10); and placebo-control is thus needed even in comparative, head-to-head RCTs to establish the effect size (10). 2) The patient's exposure to placebo in RCTs in

Table 1. Randomized controlled trials (RCTs) with 2 oral drugs (lamiditan, ubrogepant) investigating whether a second dose after 2 hours is effective in case the first dose of the drug is not effective (not pain-free [PF] at 2 h) for acute migraine treatment. For lasmiditan 100 mg, 200 mg, and placebo (4,5), and ubrogepant 50 mg, and placebo (6,7) the results from the 2 RCTs are combined, see below.

	Combined results of 2 RCTs with oral Lasmiditan (4,5)			
	Placebo (n = 1064)	Lasmiditan 50 mg (n = 556)	Lasmiditan 100 mg (n = 1035)	Lasmiditan 200 (n = 1046)
Effect of first dose, pain-free (PF) at 2 h (8).	PF = 18%	TG = 7% (2%–12%)	TG = 12% (8%–15%)	TG = 17% (13%–21%)
Effect of second dose, PF at 4 h (8).	Placebo (n = 629)	TG = −3% (−14%–7%)[X]	TG = 1% (−9%–10%)[Y]	TG = 2% (.9%−12%)[Z]
	Combined results of 2 RCTs with ubrogepant (6,7).			
	Placebo (n = 912)	Ubrogepant 25 mg (n = 435)	Ubrogepant 50 mg[2] (n = 886)	Ubrogepant 100 mg (n = 448)
Effect of first dose, PF at 2 h (9)	PF = 13%	TG = 6% (1%–12%)	TG = 7% (4%–11%)	TG = 9% (5%–14%)
Effect of second dose. PF at 4 h (9)	Placebo (n = 409)	NS, no details in abstract	TG = 15% (5%–25%)°	NS, no details in abstract

Notes: X: 20% (33/166) vs 23% (18/79); Y: 26% (67/272) vs 24% (31/125; Z: 29% (59/203) vs 26% (27/103; O: 34% (53/156) vs 19% (25/131).
TG, therapeutic gain (active minus placebo); NS, no significant difference

migraine attacks is usually limited to 2 h, after which a known, referred rescue medication is allowed (10).

In a review (11) of the ethical aspects of using placebo-control in RCTs, the importance of methodological justifications for placebo use is stressed: "To be ethical, clinical research requires balancing rigorous science with the protection of human subjects" (11).

It is, in our view, questionable to use placebo in the second step of the lasmiditan and ubrogepant RCTs for the group allocated to placebo as the initial treatment although the first placebo dose was needed in order to establish the effect size and dosage. Placebo use in a second step for initial non-responders in the intervention-arm is in principle a correct use in order to evaluate the possible effect of a second dose. Randomizing the placebo control-arm where participants are also allowed to take their preferred own rescue treatment, however, seems uninformative.

In the patients randomized to placebo as the first dose, the second "rescue dose" with placebo used by up to by 47% (1015/2174) of the control group probably only serves to "conceal the design of the clinical trial from the patients". The result is that these 1015 patients are "treated with placebo" for 4 h, whereas it is recommended by IHS that a known, preferred rescue medication should be allowed after 2 h (10). In addition, the current design where many patients were not taking the experimental second dose is not optimal, see below; and a more robust design with a separate, general efficacy RCT, and subsequent, separate RCT of rescue treatment should be used.

One important question is how the patients were informed about a possible second dose of placebo as rescue treatment. In the lasmiditan RCTs, the patients received the following information: "What will happen to you in the study? This study is set up so that you have an equal chance of being assigned to one of 5 treatment sequences to receive lasmiditan 100 mg, or lasmiditan 200 mg, or placebo for the first dose and the second dose, if needed for rescue (your migraine does not go away after 2 hours) or recurrence (your migraine goes away after 2 hours, but then comes back.)" (Provided by Eli Lilly). It is, in our view, uncertain whether the patients understood that they could be at risk of receiving placebo two times in these lasmiditan RCTs and thus whether informed consent was in fact obtained for this part of the study design. In one paper reporting an ubrogepant RCT it is stated that "all participants remained unaware of the content of the second dose" (6). In this case, patients were likely not aware of the fact that they could risk being "treated" twice with placebo only. Patients were thus not informed in detail about the risk of placebo followed by placebo treatment in trials of either treatment.

Comments on the design with 2 steps in the lasmiditan and ubrogepant RCTs. Administration of placebo twice in these RCTs is our view not ethically justified and the scientific value of randomizing the groups initially allocated to placebo can also be questioned as this step seems uninformative. There are other problems with the design of these four trials. The percentages of initial non-responders in the lasmiditan RCTs varied from 63% to 71% (4,5)and in the ubrogepant RCTs there were 71% and 80% non-responders, respectively (6,7). The non-responders could choose as rescue medication either their own preferred rescue medication or an optional second experimental dose. In the lasmiditan RCTs 46% (200 mg), 53% (100 mg), and 62% (50 mg) of non-responders took the second study dose; and in the ubrogepant RCTs 49% (50 mg), 53% (100 mg) and 56% (25 mg) of non-responders took the second dose. These patients were randomized to active drug or placebo, but it is uncertain whether one can generalize the results to the whole populations included in the trials as the reason for choosing the experimental drugs is not documented, which raises questions about self-selection bias for the ensuing comparisons.

In contrast, the use of an active dose of a triptans as the first dose followed by a second dose of the same drug or placebo in all patients (2), or the same drug or placebo in non-responders (12), resulted in much better "compliance" for the second dose. In one large RCT (n = 1086) sumatriptan 100 mg plus sumatriptan 100 mg, 80% headache relief (HR), was similar to sumatriptan 100 mg plus placebo, 77% HR, and more than 90% were treated with the planned second dose (2). In one large (n = 2800) RCT (12) 1643 non-responders to zolmitriptan 2.5 mg at 2 h were randomized to placebo, and zolmitriptan 2.5 mg or 5 mg (12) and there was similar effect in the 3 groups (12). It is remarkable that with this design, less than 1% (9/1643) of patients did not treat themselves with the second dose or were lost to follow-up (12).

Thus, with a more traditional design of a RCT for evaluating rescue medication in the treatment of migraine attacks, compliance for the second doses can be much higher than with the new design trying to evaluate both efficacy of the primary treatment and a possible effect of a second dose in the same RCT.

Conclusion

The design choice to use placebo followed by placebo in randomized trials can be questioned from an ethical standpoint and it seems uninformative. Patients should

have access to their preferred rescue medication after 2 h; and evaluation of the efficacy of a rescue dose, as done in the four trials reviewed here, does not seem motivated. A design with a first phase using the active drug or placebo and then a second phase of using the active drug or placebo in only the active arm results in only one possible administration of placebo per trial participant, and is therefore recommended.

Clinical implications

- Migraine - placebo plus placebo - not suitable design

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