Viewpoint/Perspective

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Critique of the analysis of the time course for the antimigraine effect of ubrogepant 50 mg. Clinical relevance versus statistical significance

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Peer Tfelt-Hansen[1], Anika Hüsing[2] and Hans-Christoph Diener[2]

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In an analysis of two large randomized, placebo-controlled, trials with ubrogepant, an oral calcitonin gene-related peptide (CGRP-receptor) antagonist, entitled "Time course of efficacy of ubrogepant for the acute treatment of migraine: Clinical implications" (1) Goadsby et al stated: "The full utility of an acute treatment requires examination of the entire time course of effect during a migraine attack" (1).

With regards to the time course of the effect of ubrogepant on headache, there were three observations: **I.** The of onset of effect (defined as the earliest separation from placebo) was for pain relief (PR = decrease from moderate or severe pain to none or mild) at 1 h, and for pain freedom (PF) at 2 h (Table 1). **II.** PF at 2 h is the standard primary endpoint in migraine trials recommended by the International Headache Society. The therapeutic gain (TG = verum minus placebo) of PR after ubrogepant increased from 6% at 1 h, 13% at 2 h, to 16% at 4 h, the maximum TG (1). For PF TG increased from 7% (2 h) to 17% (4 h), and to a maximum of 18% at 8 h (1). **III.** TG for sustained effect from 2–24 h was 5% for sustained freedom from pain and 16% for sustained pain relief. PF and PR separated up to 48 h with small differences (3–4%) from placebo (Table 1).

The authors conclude: **A.** "Pain relief is the most sensitive endpoint to detect early clinical effect of ubrogepant" (1). **B.** The primary end point of regulatory trials, freedom of pain at 2 h, does not provide a complete assessment of treatment effect (a hint to the increase in effect beyond 2 h?). **C.** Final statement, "the entire time course of effect is needed to understand fully the utility of ubrogepant for the acute treatment of migraine" (1).

From a clinical point of view there is a major problem with this combined post hoc analysis: the question of statistical significance versus clinical relevance. In one large trial nasal zolmitriptan 5 mg (PF = 1.4%) separated statistically from placebo (PF = 0.4%) at 15 min, without a clinical relevant difference (1% difference) (2). According to patients' priorities, clinical relevance of a trial needs to account for the time course of the effect. In two studies, the patients chose complete relief as early as 30 minutes, no adverse events, and no recurrence as their major priorities (3). Using a TG = 6% for pain relief of ubrogepant at 1 h, without any effect on pain freedom at 1 h (Table 1) as an argument for an early antimigraine effect of the drug, is hardly relevant from the patients' point of view. In the current publication headache relief is presented first as an efficacy parameter (1), followed by effect on most bothersome symptoms, and pain free. The International Headache Society recommends pain free at 2 h as the primary pain parameter; whereas headache relief at 2 h should be a secondary endpoint (4) used mainly to compare current results with results in previous clinical drug trials in migraine. In addition, the "clinical content" of pain relief varies with time. In a recent analysis of percentage of persistent mild pain/percentage of headache relief we found in 16 randomized, clinical trial (RCTs) on oral treatment of migraine

[1]Danish Headache Center, Department of Neurology, Rigshospitalet-Glostrup, Faculty of Health and Medical Sciences, University of Copenhagen, Glostrup, Denmark
[2]Institute Medical Informatics, Medical Faculty of the University Duisburg-Essen, Essen, Germany

Corresponding author:
Peer Tfelt-Hansen, Danish Headache Center, Department of Neurology, Rigshospitalet-Glostrup, DK-2650, Glostrup, Denmark.
Email: d036218@dadlnet.dk

Table 1. Time-effect curves for pain freedom (**PF**) after oral ubrogepant 50 mg [1] and oral sumatriptan 100 mg (8). Therapeutic gain (TG) for PF and 95% CI, in brackets, are calculated from (1,8). Sustained pain freedom (SPF) are values for 2–24 h (1,8).

	Pain freedom (PF)					
	1 h	2 h	4 h	24 h	48 h	SPF (2-24 h)
Ubrogepant 50 mg [1] N = 859 vs 892 placebo[a]	**PF**, TG: −1% [−3%–1%] [1]	**PF**, TG: **7%** [4%–11%] [1]	**PF**, TG: **17%** [12%–21%] [1]	**PF**, TG: **8%** [4%–12%] [1]	**PF**, TG: **4%** [1%–8%] [1]	**SPF**, TG: **5%** [2%–8%] [1]
Sumatriptan 100 mg [11]	**PF**, TG: **5%** [4% to 7%] [11]	**PF**, TG: **21%** [20%–23%] [11] [b]	[b]			**SPF**, TG: **15%** [12%–17%] [11]

Note: a, numbers at 1 h, max 886 vs 912 placebo; b, TG for PF for sumatriptan 100 mg in one RCT: 33% (2 h) and 44% (4 h), see text [9].

attacks that this percentage was 90% at 0.5 h, 72% at 1 h, 63% at 1.5 h, and 43% at 2 h (5).

Freedom from pain is a more clearly defined, more relevant clinical endpoint and more stable in time than pain relief, and PF was the primary endpoint in the two large trials, which are the basis for the current combined analysis (1,6,7). In order to evaluate a new drug treatment fairly it should be compared to a current standard treatment, see Table 1. At present there are, however, no head-to-head trials. The comparison with sumatriptan 100 mg is based on the PF results (TG's shown in bold in Table 1, from [8]) because PR is not a stable parameter over time (5), see above. We have recently suggested that onset of effect, as based on an estimate of clinical relevance, should be defined as a TG for PF $\geq 5\%$ (3), and based on this sumatriptan 100 mg has a quick onset (1 h) of effect whereas ubrogepant 50 mg (2 h) has a slow onset of effect.

Concerning efficacy, Table 1 shows, that ubrogepant 50 mg (TG = 7% for PF at 2 h) is considerably less effective than sumatriptan 100 mg (TG = 21% at 2 h), but it is mentioned that the efficacy of ubrogepant increases to a TG of 17% at 4 h [1]. In one RCT rescue medication was first allowed after 4 h, and the TG for PF for sumatriptan 100 mg was 33% (95% confidence interval [CI]: 24% – 40%) at 2 h and 44% (95%CI: 33%-52%) at 4 h (10).

Based on sustained pain freedom at 2-24 h and PF effects at 24 h and 48 h ubrogepant 50 mg is claimed to have a long duration of effect (1). For this claim the authors present results based on imputed data, but the proportion of real observed data at different time-points is unclear, and supposedly small as stated: "multiple imputation is based on a low percentage of available data" (1). Proportions of PF or PR at 2h vs. sustained PF or PR 2-24h reveal only a limited proportion of sustained success (in the original publications [6,7]), but in "last observation carried forward"-imputation the symptoms are assumed to be stable. A considerable proportion of patients has used secondary and/or rescue medication (again, see original publications [6,7]), which indicates symptom change for the worse. However, adjustment for extra-medication through censoring and imputation did not account for deterioration of symptoms. The data display does not inform about potential optimism from the applied imputation methods. The authors state as a limitation that "both methods introduce bias in different ways", but simple additional sensitivity analyses setting missing data to non-response (as performed in the original publications) were omitted (1). Therefore, the reported evidence for long-term effects remains questionable.

In conclusion, when evaluating the time course of ubrogepant 50 mg the primary efficacy measure should be pain freedom, a clinically relevant measure (confer the wishes of the patients), which is stable over time. Pain freedom (TG = 7%) after ubrogepant 50 mg is first observed at 2 h in large placebo-controlled RCTs. Therefore, ubrogepant has a slow onset of action and a low effect compared to placebo and sumatriptan.

The increase of efficacy (increase of therapeutic gain) beyond 2 h is not specific to ubrogepant, but observed for most acute migraine drugs such as triptans and non-steroid anti-inflammatory drugs (NSAIDs); (9). The imputed long-term data presented by Goadsby et al (1) may be too optimistic and is not reliable.

Clinical Implications

- Migraine patients want early pain-free, not headache relief.
- Imputation of missing data up to 24–48 h is very uncertain.

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ORCID iD

Hans-Christoph Diener https://orcid.org/0000-0002-6556-8612

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