COMMENTARY

Is there an inherent limit to the efficacy of calcitonin gene-related peptide receptor antagonists in the acute treatment of migraine? A comment

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Abstract Calcitonin gene-related peptide (CGRP) receptor antagonists are a new treatment principle in acute migraine attacks. Intravenous olcegepant 2.5 mg resulted in 66% headache relief after 2 h, whereas subcutaneous sumatriptan resulted in 81–92% headache relief after 2 h. The intrinsic activity of a parenteral triptan, a 5HT_{1B/1D} receptor agonist, is thus higher than the maximum effect of the parenteral CGRP receptor antagonist olcegepant. For the orally bioavailable CGRP antagonist telcagepant 300 mg, the headache relief was only 55% in one phase III study. These results indicate that CGRP receptor antagonist in success in the acute treatment of migraine in only a certain fraction of the patients.

Introduction

The involvement of calcitonin gene-related peptide (CGRG) in migraine is shown by the fact that CGRP infusion causes migraine without aura in migraineurs [1]. In addition, the two CGRP antagonists, olcegepant and telcagepant, are effective in the acute treatment of migraine [2–4]. A major advantage of CGRP antagonists compared with the triptans, is the lack, so far, of clinically important vascular adverse events [2–4].

The efficacy of oral drugs such as triptans and CGRP antagonists in the acute treatment of migraine most likely

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P. C. Tfelt-Hansen Department of Neurology, University of Copenhagen, Glostrup, Denmark depends on several factors such as bioavailability [5], Tmax [5], lipophilicity and intrinsic activity/blocking efficacy. Triptans are 5-HT_{1B/1D} receptor agonist and by increasing the parenteral dose of a triptan used in randomised clinical trials (RCTs) one can get an estimate of the intrinsic activity of the drug.

One cannot directly compare the results of a receptor agonist such as a triptan with that of a receptor antagonist such as the CGRP antagonists, olcegepant and telcagepant. Whereas the maximum effect of an agonist depends on its intrinsic activity, the efficacy of the receptor antagonist apart from its blocking potency also depends on the involvement of the biological agonist it is presumed to block, in the migraine process. If the biological agonist is not the only factor involved in the migraine process, one cannot expect the antagonist to cure all cases.

Review of some randomised clinical trials with triptans and CGRP antagonists

Intrinsic activity of triptans in acute migraine treatment

The maximum effect of a triptan has been shown for subcutaneous naratriptan 10 mg for which 88% pain-free response after 2 h was found in one RCT [6, 7]. This very high pain-free response comes with a penalty of 71% adverse events (AEs) [6]. For subcutaneous sumatriptan 6 mg, the pain-free response was 55% and the AEs were 53% [6, 7]. In contrast, sumatriptan 6 mg (81%, 86%, 89%, 92% [6, 8, 9]) and naratriptan 10 mg (91%) resulted in quite similar headache relief (a decrease from moderate or severe to none or mild) after 2 h [6]. Headache relief has been the primary efficacy measure in many RCTs [8–10]

and is still widely used [2–4] and will therefore be used in the following.

For the most effective triptan form used clinically, subcutaneous sumatriptan 6 mg, the therapeutic gain (TG) (percentage response with active drug minus response with placebo) for headache relief is 51% (95% CI, 48–53%) after 1 h [10]. For oral sumatriptan 100 mg the TG is 33% (95% CI, 31-35%) after 2 h [10]

Effect of CGRP receptor antagonists in acute migraine treatment

In the olcegepant RCT from 2004 the headache relief for 2.5 mg olcegepant, a very potent calcitonin gene-related peptide (CGRP) antagonist [11, 12], intravenously was 66% after 2 h but only 46% after 1 h, [2]. These response rates and Fig. 1 illustrate, for an intravenous drug, the rather slow onset of action of olcegepant. The corresponding TG was 39% (2 h) and 32% (1 h), respectively [2].

In the case of olcegepant it has been estimated that the dose used, 2.5 mg, is about 1,000 times the concentration needed for peripheral blockade of CGRP [13]. There should therefore most likely, even in theoretical deep departments such as beyond the BBB, be enough CGRP blocker present to block the effect of CGRP. This is supported by the results in cats [14]. Olcegepant caused a dose-dependent inhibition of superior sinus sagittalisevoked activity in trigeminal nucleus caudalis with an ED50 of 31 μ g/kg [14]. This corresponds to 2.1 mg/70 kg and is thus near the chosen optimal therapeutic dose of olcegepant 2.5 mg intravenously [2].

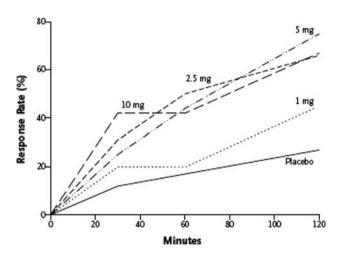


Fig. 1 Rates of headache relief after 10 min intravenous infusion of olcegepant 1–10 mg or placebo according to the time after start of the infusion. From [2] with permission

Furthermore, in a human study olcegepant 2.5 mg completely blocked the majority of the effects of h- α CGRP infused in a high dose of 1.5 µg/min [15]. Thus, CGRP receptor blockade in the migraine study [2] must most likely have been nearly complete. It should be noted that 10 mg olcagepant did not result in more patients with headache relief (68%) than after 2.5 mg (66%) [2]. Thus, the effect of intravenous olcegepant 2.5 mg is most likely near the maximal effect one can expect of a CGRP antagonist in migraine.

The first orally bioavailable CGRP receptor antagonist, telcagepant, has been studied in two RCTs [3, 4]. After a dose-defining RCT [3] telcagepant 300 mg was chosen as the optimal dose in a phase III RCT [4].Clinically the effect of telcagepant in the phase III study [4] was not that impressive [16]. Thus, the 2 h pain freedom was 27% for telcagepant 300 mg versus 10% for placebo and headache relief was 55 and 28%, respectively [4]. The TG for telcagepant for headache relief was thus 27% (95% CI, 20–34%) apparently similar to the TG for oral sumatriptan 100, 33% (95% CI, 31–35%), but more data on telcegepant are needed.

How high a dose is telcagepant 300 mg, the absolute headache relief was 67% for 300 mg, 400 mg and 68% 600 mg in a relatively small dose-defining RCT with a high placebo response of 46% [3]. Thus, doubling the dose from 300 to 600 mg did not increase efficacy and the efficacy of the 300 mg dose is probably near the maximal effect of telcagepant.

Conclusion

When given intravenously, the potent CGRP receptor antagonist olcegepant 2.5 most likely results in a maximal effect in the treatment of acute migraine [2]. Despite the optimal dosage form, the headache relief was 46% after 1 h and 66% after 2 h, considerably less than the 70% after 1 h and 81–92% after 2 h for subcutaneous sumatriptan 6 mg [6, 8, 9]. The intrinsic activity of the most potent clinically used triptan, subcutaneous sumatriptan 6 mg, is thus higher than the maximal effect of the intravenously used CGRP antagonist, olcagepant 2.5 mg.

This indicates that there is most likely an inherent limit to the response one can expect from CGRP receptor antagonist, such as olcegepant and telcagepant, in the acute treatment of migraineurs as a group.

One possible hypothetical explanation for this is that CGRP is not involved in the final steps of the pathophysiological process of migraine. Instead these final steps in the pathophysiological process of migraine could involve nitric oxide [17].

Conflict of interest None.

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