**CGRP ANTIBODIES WILL BECOME THE TREATMENT CHOICE FOR CHRONIC MIGRAINE - CON**

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CGRP is widely accepted as the key neuropeptide in the generation of migraine pain and is hence in the focus as a main target for migraine therapy. CGRP causes arterial vasodilatation enhancing neurogenic inflammation in the meninges but CGRP is also an important neuromodulator at the first synapse of trigeminal afferents in the trigeminal nuclear complex. Several other binding sites of CGRP in the brain indicate additional central effects. Whether or not a central action of CGRP is important for releasing or aggravating migraine pain is a matter of ongoing debate. Since it is not likely that intracranial vasodilatation itself is a noxious stimulus causing headaches and because CGRP is not activating nociceptors, a peripheral action appears questionable. Independent of that, pharmacotherapeutic interventions blocking either CGRP release (triptans), CGRP binding (gepants) or CGRP molecules (aptamers and antibodies) have shown direct or indirect efficacy in acute clinical or experimental trials. However, an effective treatment for chronic migraine based on suppression of CGRP actions appears problematic. It is not very likely that CGRP antibodies will become the choice of treatment for chronic migraine because of two major reasons.

First, CGRP can presumably exert central actions only if it is released from intracerebral nerve fibers. It is not known if and to which extent CGRP can penetrate the blood-brain barrier but it is likely that CGRP is drained rather from the brain than into the brain. There is experimental evidence that most of the CGRP released from intracranial afferents accumulates in the cerebrospinal fluid, while much less appears in the venous outflow. Moreover, CGRP levels in the circulation are probably too low to have any effect on the trigeminovascular system. Antibodies, on the other hand, bind the circulating CGRP but it appears questionable that they penetrate the brain easily.

Second, CGRP receptors are expressed in multiple extracerebral organs, where CGRP seems to have mainly protective functions. It has inotropic effects in the heart and can prevent pressure-induced heart failure, it exhibits anti-inflammatory properties in the liver, and it contributes to immunoregulatory functions for example in the eye. Thus chronic inhibition of CGRP may have severe unwanted side-effects. There is no reason to assume that these side effect are different from those experienced with telcagepant, the daily use of which has caused an increase of transaminases presumably through inhibition of CGRP receptors in the liver.