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VIEWPOINT

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ACS Chemical Neuroscience Molecule Spotlight on Telcagepant (MK-0974)

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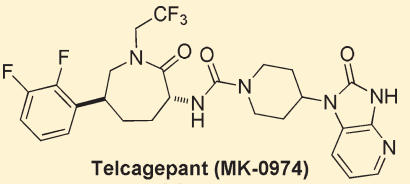
ABSTRACT: Telcagepant (MK-0974) is a novel calcitonin gene-related peptide (CGRP) receptor antagonist currently undergoing clinical trials for migraine (http://www.merck.com/research/pipeline/home.html). MK-0974 is currently being studied in phase III clinical trials.



Telcagepant (MK-0974)
Merck's CGRP antagonist

It is estimated that more than 15% of the adult population in developed countries suffer from migraines, a neurological and neurovascular disorder.[1] Migraines are characterized by severe and often debilitating headaches often accompanied by several issues such as nausea, vomiting, and heightened sensitivity to light and sound. These attacks generally are unilateral and can cause intense throbbing and pulsing that can last from hours to days in length and are much more common in women than in men (~3:1). The exact cause of migraines is still elusive to researchers; however, it is thought that a combination of genetics and environmental factors (such as food, stress, changes in sleep patterns, etc.) plays a major role.[2] Current treatments for migraines are common pain relievers (ibuprofen, acetaminophen) for mild migraines and triptans for more severe migraines. Triptans (such as imitrex) are agonists of serotonin receptors and have been effective in relieving pain, nausea, and external sensitivities associated with migraines. Unfortunately, although triptans are the drug of choice for acute migraine specific treatment, many studies have shown that a significant amount of the treated population do not respond to this drug class.[3] Due to these shortcomings, significant research has been devoted to discovering and developing better treatments for migraines.

One promising class of compounds that has emerged is antagonists of the calcitonin gene-related peptide (CGRP) receptor for treatment of acute migraines. CGRP is a member of the calcitonin family of peptides and exists in both the α- and β-forms. α-CGRP is a 37-amino-acid neuropeptide that is widely distributed in the central and peripheral nervous systems and one of the most abundant peptides. CGRP is a peptide vasodilator and can function in the transmission of pain. A number of studies have shown the importance of CGRP in migraines. First, it has been reported that CGRP concentrations in the cranial circulation are increased,[4] and second, migraine suffering patients that have been given CGRP have reported migraine-like symptoms after administration.[5]

Merck Research Laboratories has reported on a novel, orally bioavailable CGRP antagonist, telcagepant (MK-0974). MK-0974 is an extremely potent antagonist with a K_i = 0.77 ± 0.07 nM.[6] MK-0974 was also very potent in a cell-based assay measuring inhibition of CGRP-stimulated cAMP production (IC_{50} = 2.2 ± 0.3 nM), which was only shifted 5-fold (IC_{50} = 11 ± 2.1 nM) in the presence of 50% human serum, suggesting a modest level of protein binding.[6] MK-0974 displayed acceptable in vivo PK values with low clearance in the rat (9.4 mL/min/kg) and moderate half-life (1.6 h) and moderate clearance in the dog (17 mL/min/kg). These PK values translated into acceptable levels of bioavailability in rats (20%) and dogs (35%).[6] Lastly, MK-0974 was evaluated in an in vivo pharmacodynamic rhesus study.[6] MK-0974 was potent in this model (EC_{50} = 120 nM; EC_{90} = 1000 nM) and also had low clearance (7.0 mL/min/kg) and good half-life (2.8 h) in rhesus.[6] MK-0974 also showed excellent selectivity against a panel of >160 receptors, transporters, and enzymes.

Recently, the results of a large, randomized, placebo-controlled, parallel-treatment trial were published.[7] In this study, 1380 patients were randomly assigned telcagepant (150 mg or 300 mg), zolmitriptan (5 mg), or placebo. It was determined from this study that telcagepant (300 mg) was more effective than placebo for pain freedom, pain relief, and absence of audio or visual effects and nausea, and was comparable to that of zolmitriptan (5 mg). Both were more effective than the 150 mg dose of telcagepant. However, adverse events for 300 mg telcagepant (37%) were much lower than those for zolmitriptan (51%) and were comparable to the adverse events with placebo (32%). The highest side effect prevalence for telcagepant was dry mouth (6%), whereas for zolmitriptan it was dizziness (11%). The overall conclusions of this study were telcagepant was as effective as zolmitriptan for acute treatment of migraines, but with fewer associated side effects.

Two additional reports show somewhat conflicting data on the efficacy of telcagepant.[8,9] This first report shows that 27% of patients respond to telcagepant whereas 33% of Sumatriptan patients respond and 40% of rizatriptan respond to being pain

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free after 2 h.[8] The second report, however, looked at the response rates of individuals that respond to triptans and those that do not.[9] These results show that those patients that respond to triptans were pain free after 2 h with zolmitriptan (44%) but that only 14% of those patients that previously did not respond to triptans were pain free. These same patient populations were treated with telcagepant and showed a lower efficacy with the triptan responding group (23%); however, telcagepant showed a higher response rate (29%) for the group that did not respond to triptans.

These studies all show that telcagepant is well-tolerated and shows efficacy against acute migraines; however, it indicates that different patient populations may show more beneficial effects with telcagepant versus triptans. As telcagepant (MK-0974) is still under evaluation, it may take a while before the full dosing regimen is elucidated for this promising candidate for those that suffer from migraines.

REFERENCES

(1) Stovner, L. J., Hagen, K., Jensen, R., Katsarava, Z., Lipton, R. B., Scher, A. I., Steiner, T. J., and Zwart, J.-A. (2007) The global burden of headache: a documentation of headache prevalence and disability worldwide. *Cephalalgia 27*, 193–210.

(2) Gervil, M., Ulrich, V., Kaprio, J., Olesen, J., and Russell, M. B. (1999) The relative role of genetic and environmental factors in migraine without aura. *Neurology 53*, 995–999.

(3) Edvinsson, L., and Linde, M. (2010) New drugs in migraine treatment and prophylaxis: telcagepant and topiramate. *Lancet 376*, 645–655.

(4) Goadsby, P. J., Edvinnson, L., and Ekman, R. (1990) Vasoactive peptide release in the extracerebral circulation of humans during migraine headaches. *Ann. Neurol. 28*, 183–187.

(5) Lassen, L. H., Haderslev, P. A., Jacobsen, V. B., Iversen, H. K., Sperling, B., and Olesen, J. (2002) CGRP may play a causative role in migraine. *Cephalalgia 22*, 54–61.

(6) Paone, D. V., Shaw, A. W., Nguyen, D. N., Burgey, C. S., Deng, J. Z., Kane, S. A., Koblan, K. S., Salvatore, C. A., Mosser, S. D., Johnston, V. K., Wong, B. K., Miller-Stein, C. M., Hershey, J. C., Graham, S. L., Vacca, J. P., and Williams, T. M. (2007) Potent, orally bioavailable calcitonin gene-related peptide receptor antagonists for the treatment of migraine: discovery of *N*-[(3*R*,6*S*)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (MK-0974). *J. Med. Chem. 50*, 5564–5567.

(7) Ho, T. W., Ferrari, M. D., Dodick, D. W., Galet, V., Kost, J., Fan, X., Leibensperger, H., Froman, S., Assaid, C., Lines, C., Koppen, H., and Winner, P. K. (2008) Efficacy and tolerability of MK-0974 (telcagepant), a new oral antagonist of calcitonin gene-related peptide receptor, compared with zolmitriptan for acute migraine: a randomised, placebo-controlled, parallel-treatment trial. *Lancet 372*, 2115–2123.

(8) Tfelt-Hansen, P. (2011) Excellent tolerability but relatively low initial clinical efficacy of telcagepant in migraine. *Headache 51*, 118–123.

(9) Ho, T. W., Olesen, J., Dodick, D. W., Kost, J., Lines, C., and Ferrari, M. D. (2011) Antimigraine efficacy of telcagepant based on patient's historical triptan response. *Headache 51*, 64–72.