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Highlights in Headache in 2014

There have been important studies on migraine in 2014 (1). Firstly, there has been significant advancements in development of the antibodies targeting calcitonin gene-related peptide (CGRP). First reports on the effectiveness of the 2 out of 4 biological agents that have been currently under development have been published. In addition, FDA approved three different medical devices for the treatment of migraine within the past 12 months. These are the first medical devices that were approved for the treatment of migraine. Lastly, for the first time after the year 2000, American Headache Society published a review on the evidence-based evaluation of migraine drugs (2). In summary, 2014 was a year of paradigm shifts with the development of biological CGRP antagonist and the application of medical devices in migraine treatment. Ongoing studies on migraine can be reached on "Clinicaltrials.gov".

Cerena Transcranial Magnetic Stimulator (TMS) Device: In November 2013, FDA approved the use of device to relieve the pain in migraine with aura. The recommended daily usage limit is one application in 24 hours. This device has not been made available on the market yet and the company has developed a more compact version of it. Cerena TMS device has been found to be superior to placebo in the randomized, double-blind, parallel group clinical study on migraine with aura. One hundred sixty patients received applications with one active (n=82) or sham (n=82) device in at least one attack. The rate of painlessness was higher in the active group (39%) versus sham group (22%) within the next two hours. Painlessness responses in the next 24 and 48 hours following the treatment are significantly better and there were no reported side effects of the treatment (3). However, there were no improvement in symptoms associated with migraine such as photophobia, photophobia and vomiting. In addition, FDA did not recommend the device for people who have metal in their head, neck, torso, those who have deep-brain stimulation, pace-makers, those who are under risk for epilepsy risk or those with a familial history of seizures.

Spring Transcranial Magnetic Stimulator (TMS) Device: A second-generation device produced by the same company that produced the first device. It provides similar treatment options but it is easier to carry. It was approved by FDA in May 2014 for clinical use.

Cefaly Transcutaneous Electrical Nerve Stimulation Device: This device consists of battery-operated, reusable and replaceable electrodes that are placed above the eyes in order to apply a continuous 14 mA current directly on the supraorbital cutaneous nerve. The device is used for 20 minutes every day to reduce the migraine attack frequency and it is the first device approved by FDA for migraine prophylaxis in May 2014. Its effectiveness and safety were evaluated in a double-blind, randomized and sham-controlled study with people who have more than 2 migraine attack every month (4). When the participants used the device every day for 20 minutes for 3 months, the number of migraine days, monthly migraine attack counts, monthly headache days and the number of medicine taken for acute migraine attacks decreased significantly in the active group compared to the control group. The satisfaction rate for Cefaly treatment was 53% and the participants reported that they were planning on purchasing the device to continue the treatment. The most common side effects were the unpleasant sensation from the electrical stimulation, sleepiness during the treatment session and the ensuing headache. No serious side effects were reported in the study.

LY2951742 (Human CGRP Antibody): The randomized, double-blind, placebo-controlled phase II study on this molecule was published in 2014 (5). People who experience migraine attacks in 4-14 days in a month received subcutaneous LY2951742 (n=107), or placebo (n=110) for 12 weeks. The primary outcome of the study was the decrease in the mean number of days with migraines in one

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month. When the 12th week status was compared to the starting point, LY2951742 was found to be superior to placebo (-4.2, 63% and -3.0, 42%). In addition, the LY2951742 treatment performed more effectively than migraine in the secondary outcomes of the study, which were "number of days with headache" (-4.9 and -3.7; p=0.0117), "migraine attacks" (-3.1 and -2.3; p=0.0051) and "responsiveness ratio" (70% and 45%). However, the side effects of the treatment were more severe than the placebo's. These included pain on the injection site, upper respiratory tract infection and stomachache. The researchers concluded that LY2951742 treatment is effective and well tolerated in people with frequent migraine attacks (5). Two new studies were launched with this molecule in 2014.

ALD403 (CGRP Antibody): In this randomized, double-blind, placebo-controlled study that investigated the effectiveness and safety of the monthly application of this molecule, migraine patients who experience 5-14 days of migraine in 28 days (n=163) received either ALD403 or placebo as one dose (6). The difference in average number of days with migraine at the 5-8th weeks compared to the starting point was found to be -5.6 for ALD403 and -4.6 for placebo (difference was -1; p=0.031). Side effects were seen in 57% in ALD403 group and 52% in placebo group. There was no reported safety issues associated with 1000 mg intravenous application of ALD403. The researchers concluded that ALD403 has limited evidence of being effective in preventive treatment against migraine (5). A new study using this molecule with chronic migraine patients was launched in 2014.

LBR-101 (Human CGRP Antibody): Two studies, scheduled to finish in 2014 and 2015, were launched with this molecule. The first one investigated the effectiveness and safety of LBR-101 in the preventive treatment against migraine as compared to placebo whereas the second one is comparing the prophylactic use of LBR-101's two dose against placebo in frequent episodic migraine.

AMG 334 (Selective Human CGRP Receptor Antibody): The difference of this molecule from the previous three agents is that it is a selective human monoclonal antibody developed specifically against CGRP receptor complex, as opposed to CGRP itself. In theory, the ability to block CGRP receptor (instead of CGRP) can be more advantageous since binding onto CGRP receptor may both inhibit the receptor's activation and the production of CGRP. There are completed phase 1 and ongoing phase 2 studies on this molecule. However, the results have not yet been published.

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The Effect of Intra-arterial Thrombolysis in Proximal Anterior Circulation Ischemic Stroke

Interventional Management of Stroke (IMS III) study was terminated early after discovering that endovascular intervention following intravenous (iv) thrombolysis does not provide an extra benefit (1). In this study, 656 acute ischemic stroke patients who underwent iv. thrombolysis were randomized into two groups within the first three hours and one group received an additional endovascular intervention. During the study, it was seen that the 90th day modified Rankin (mRankin) scores did not differ between the two groups. The fact that the disability between the two groups was not different despite the higher rate of revascularization in the endovascular intervention group caused a level of pessimism in the centers that frequently administer interventional treatment.

A similar attempt to disentangle this contradiction was performed in 16 centers in the Netherlands and was published in January 2015 in New England Journal of Medicine. In this trial coined "Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands" (MR CLEAN), the researchers randomized 500 acute anterior circulation stroke patients into two groups with 1:1 ratio, and gave standard treatment to one group while administering endovascular intervention to the other group within 6 hours.

89% of the participants received iv. alteplase treatment. The mean age of the patients was 65 (age range 23-96). The study included only patients with distal intracranial carotid artery, M1, M2, A1 or A2 occlusion and NIHSS score above 2. Third generation, retractable stents were used in 82% of the patients. The method of endovascular intervention, intra-arterial thrombolytic (alteplase or urokinase) use, thrombus aspiration or stent use was left onto the discretion of the clinician. The first outcome of the study was the mRankin score on the 90th day and the second outcome was the improvement in NIHSS score and radiological parameters in the 24th hour, 5th and 7th days.

At the end of the study, 33% of the endovascular treatment group and 19% of the control group had mRankin scores lower than 2 (shared HR: 1.67; safety interval 1.21-2.30). Symptomatic intracranial bleeding and mortality rates were found to be equal in both groups. Retractable stents were used in 82% of the patients who received endovascular intervention. Intra-arterial thrombolytic treatment was used in only 10% of the patients assigned to endovascular intervention group. It was understood that 13% of the patients in the study also received acute carotid stenting. While 75% of the endovascular treatment patients showed revascularization, this rate was 33% in the control group.

MR CLEAN study resulted with contradictory results with IMS III, and a possible cause might be that people were randomized much earlier in the IMS III study, accentuating the effect of iv. thrombolysis while diminishing the difference between the groups. Another possible difference between the studies that might explain the discrepancy in results could be

that MR CLEAN study included only the patients with anterior system and proximal artery blockage. The increased use of the new endovascular treatment devices for acute stroke suggests that repetition of the earlier studies that resulted in negative outcomes may have different outcomes if they are repeated.

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