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New therapeutic options in migraine treatment

1. Aleksandra Kłos [AK]

Student Scientific Association at Department of Epidemiology and Clinical Research Methodology, Medical University of Lublin, ul. Radziwiłłowska 11, Lublin 20-080, Poland
https://orcid.org/0009-0008-6870-2590
aleksandra.kloss@interia.pl

2. Mateusz Pawlicki [MP]

Kardynał Stefan Wyszyński Province Specialist Hospital in Lublin, Kraśnicka 100 avenue, 20-718 Lublin, Poland
https://orcid.org/0000-0001-8318-6573
pawlak32@gmail.com

3. Karol Stachyrak [KS]

Independent Public Health Care Center in Łęczna Krasnystawska 52 street, 21-010 Łęczna, Poland
https://orcid.org/0009-0008-3175-1866
karol.stachyrak@gmail.com

4. Dawid Mika [DM]

1st Military Clinical Hospital with SPZOZ Polyclinic in Lublin, Racławickie 23 avenue, 20-049 Lublin, Poland
https://orcid.org/0009-0003-5254-5344
mikadawid@gmail.com

5. Bartosz Mazur [BM]

Kardynał Stefan Wyszyński Province Specialist Hospital in Lublin, Kraśnicka 100 avenue, 20-718 Lublin, Poland
https://orcid.org/0000-0003-0601-4350
bartoszmazur27@gmail.com

6. Kamila Turek [KT]

Medical University of Lublin, Racławickie 1 avenue, 20-059 Lublin, Poland
https://orcid.org/0009-0000-6888-8913
kamila.turek26@gmail.com

7. Maciej Lambach [ML]

Kardynał Stefan Wyszyński Province Specialist Hospital in Lublin, Kraśnicka 100 avenue, 20-718 Lublin, Poland
https://orcid.org/0009-0004-3348-4272
mlambach97@gmail.com

8. Anna Greguła [AG]

Independent Public Health Care Center in Łęczna Krasnystawska 52 street, 21-010 Łęczna, Poland
https://orcid.org/0009-0007-3712-7960
aniagregula19@gmail.com

9. Aleksandra Mazurek [AM]

Student Scientific Association at Department of Epidemiology and Clinical Research Methodology, Medical University of Lublin, ul. Radziwiłłowska 11, Lublin 20-080, Poland
https://orcid.org/0009-0007-5298-782X
amazurek2702@gmail.com

10. Wiktoria Wilanowska [WW]

Kardynał Stefan Wyszyński Province Specialist Hospital in Lublin, Kraśnicka 100 avenue, 20-718 Lublin, Poland
https:/orcid.org/0009-0000-8388-8479
wiktoria.wilanowska@gmail.com

ABSTRACT

Keywords: migraine; ditans; gepants; migraine treatment

Introduction and purpose

Migraine is a common disease mostly affecting women. It has a huge influence on patients' life strongly decreasing its quality by cause of repetitive headache episodes and often comes with unpleasant and burdensome symptoms like photophobia, nausea or vomiting. This article focuses on migraine treatment, especially on new drugs. Primary drugs used in migraine attacks are non-steroid anti-inflammatory drugs (NSAI) and triptans. Because of their side effects and

impact on internal organs, these substances are often contraindicated or inefficient. The same applies to triptans, which cannot be used by patients with cardiovascular diseases. Due to the need of a new migraine treatment path development, new remedies have been found, bringing hope for patients who could not use prior options. They are divided into two groups: ditans (lasmiditan), which are 5-HT1F serotonin receptor agonists and gepants (ubrogepant, rimegepant, atogepant and zavegepant), which are CGRP receptor antagonists. A summary of the current state of knowledge is intended to increase the awareness of physicians and patients when selecting the appropriate treatment.

Material and methods

The following review was based on articles obtained from the PubMed and Google Scholar databases. Key search terms included migraine, ditans, gepants, migraine treatment.

Conclusions

Drugs described in this study clearly show the new pathway of migraine treatment and prevention. They are safer and show more benefits than substances currently used. They can also be used in wider range of patients with conditions marked as contraindications for current schemes. However more research is still needed to fully describe their characteristics.

New therapeutic options in migraine treatment:

Introduction:

Migraine is characterized by unilateral, pulsating headache lasting 4 to 72 hours often occurring with photophobia, osmophobia, nausea or vomiting. About 11-12% of Europe and North America's population is influenced, most of which are women (75%). (1) The disease peak incidence occurs between the age of 25 and 55. It is a common cause of disability causing huge personal and socio-economical burden as well as lowering one's quality of life. Migraine can manifest as migraine without aura (MO) or migraine with aura (MA) which is characterized by visual, sensoric, motoric or other central nervous system symptoms preceding headache. (2) The

condition's pathophysiology is not well known. Literature mentions that an important role in its development play vasoactive substances and neurotransmitters like calcitonin gene-related peptide (CGRP), neurokinin A, Substance P or nitric oxide. They interact with vessel wall causing its dilation, protein extravasation and sterile inflammation. Trigeminocervical complex stimulation caused by these compounds is later transferred to thalamus and cortex where the pain is registered. (3) Migraine consists of few phases: prodromal, aura phase, headache and postdromal. In the first one, preluding symptoms such as fatigue, anxiety, photophobia, increased hunger or yawning occur. Aura phase, as previously stated, is related to temporary neurological deficits and in the postdromal phase the patient is free from pain, but can still suffer from tiredness and unpleasant feeling. (4) Migraine is also often a familial disease and can be inherited. Genetic studies have shown that migraine risk is linked with multiple genes. Finding 38 migraine susceptibility loci, migraine risk variants were enriched in genes related to vascular and visceral smooth muscle.(5–7)

Methodology

The following review of studies was based on articles obtained from the PubMed and Google Scholar databases. Key search terms included migraine, ditans, gepants, migraine treatment.

State of knowledge

Migraine treatment can be split into acute headache attack interrupting drugs and prevention aiming for decrease in frequency, strength and duration of the attacks. Medicines used in migraine attacks are usually non-steroidal anti-inflammatory drugs, paracetamol, acetylsalicylic acid, 5HT1b/1d receptor agonists and dopamine receptor antagonists. They should be given as early as possible, when the headache is mild. (8) Prevention however mainly uses beta-blockers (propranolol, metoprolol), antidepressants (amitriptyline), antiepileptic drugs (topiramate, valproate) and monoclonal antibodies targeting CGRP receptors (fremanezumab, erenumab, galcanezumab). (9) Elemental drugs used in migraine attacks treatment (NSAI) cannot be administered to all patients because of their side effects on stomach or kidneys. They also show no effects in some part of the population. Another huge drug group, 5HT1b/1d receptor agonists called triptans (sumatriptan, zolmitriptan,

naratriptan, rizatriptan) also has significant drawback connected with their mechanism of action by inhibiting vasoactive peptides secretion, vasodilation and suppressing pain pathways in brainstem. They are therefore prohibited in patients with in increased cardiovascular risk (ischemic heart disease, uncontrolled hypertension or peripheral vessels disease.). (10) The following group, ergot alkaloids (ergotamine and dihydroergotamine), is associated with rapid headache development after their overdosage, adverse effects on cardiovascular system and lower efficiency than triptans. (11) A headache mentioned before is an important issue in the use of current emergency treatment for migraine seizures is called the medication overuse headache (MOH). This situation is very unfavorable for the patient, as migraines are becoming increasingly resistant to treatment. For this reason, it is necessary to look for therapies and new options that will not cause such effects. (12,13) Another problem limiting current migraine treatment is the recurrence of headaches after an initial response to treatment especially with triptans. (14) As a result of the need of new treatment methods discovery for patients in whom all the options mentioned above cannot be used or are ineffective, in the last couple of years a significant breakthrough in acute migraine attacks treatment occurred. One of the examples are monoclonal humanized or fully human antibodies against CGRP peptide or CGRP receptor, more specifically gepants (rimegepant, atogepant, ubrogepant). Another example are 5-HT1f receptor agonists- ditans (lasmiditan). (15) Because of such big increase in therapeutic options availability, this review will focus only on the new drugs lately approved by the Food and Drug Administration (FDA).

Serotonin 5HT1F agonists – the Ditans:

The only drug available in this group is lasmiditan, approved in 2019. It is thought, that it inhibits CGRP releasing in peripheral and central trigeminal nerve endings. Moreover, because of its blood-brain barrier penetrability it probably has some nociceptive outcome. Preclinical trials also showed that it reduces trigeminovascular activation and suppresses superior salivatory nucleus activation in the trigeminal autonomic reflex. (16) Its huge upside is that it can be used in elderly people and in patients with increased cardiovascular risk, because receptors it has impact on are not found in vascular muscles (like triptane receptors) and

therefore no dilation can be observed. This drug is rapidly absorbed and reaches its plasma peak concentration in an average of 1,8 hour. A single dose varies from 50 to 200 milligrams. (1)

Its safety and effectiveness has been proved in prospective, randomized, double-blind, placebo-controlled and multicentre phase 3 study in patients with and without aura. Participants were mainly middle-aged white women with migraine, most of whom had at least one cardiovascular risk factor. They were told to use lasmiditan in single migraine attack treatment (moderate to severe) for 8 weeks since enrollment in outpatient basis. Having been divided into groups, patients were given the medicine in 50mg, 100mg or 200mg doses or placebo. A percentage of people in whom headache and accompanying symptoms (photophobia, nausea or phonophobia) disappeared in 2 hours after intake was calculated. Participants received electronic diaries to note information about headache onset time, its intensity and additional symptoms before the medication intake and 48 hours (in adequate time periods) or 72 hours (if the next dose had been administrated more than 24 hours later) afterwards. At the end of the trial it was found that all of the lasmiditan doses made the headache and MBS (most burdensome symptom) disappear in significantly higher percentage than in placebo. As it comes to TEAE (treatment emergent adverse events), proportion of patients reporting them was higher in research group than in placebo and was connected with the dose (the highest in 200mg – 39%, 100mg – 36,2%, 50mg – 25,5%, placebo – 11,6%). The most frequent TEAEs were dizziness, sleepiness and paresthesia. The prevalence of ones combined with cardiovascular diseases was low (0,5%). Higher doses were associated with headache-free time after just one hour and MBS-free time after 0,5 hour since the intake. What is more, effects like phonophobia and photophobia ceased. This effect however did not involve nausea. (17) It is also important, that if the first dose fails, second one does not bring significant benefits and because of psychomotor performance impairment, it is forbidden to drive any vehicles for 8 hours after medicine intake. Due to action on serotonin receptors, a possible serotonin syndrome development must be kept in mind while using other substances increasing this risk. (16) This new group of drugs opens treatment pathways for elderly and patients with cardiovascular diseases like coronary heart

disease or hypertension in which triptans therapy would not be possible and therefore migraine might not be treated properly.

Small Molecule CGRP Receptor Antagonists – The "Gepants":

Drugs in this group are CGRP receptor or ligand antagonists. The first generation had appeared to be strongly hepatotoxic what concluded research on them. After several years, trials on second generation started and it turned out to be very effective in migraine treatment. This applies to: ubrogepant, rimegepant and atogepant. They have very good bioavailability, cause little side effects and, what is important, do not affect vasoconstriction. Third generation of gepants consists of zavegepant which is examined for subcutaneous, oral or nasal administration. (3)

Ubrogepant:

Ubrogepant has been approved by the FDA as the first gepant to treat acute migraine attacks with or without aura in 2019. (16) Its safety and efficiency have been proven in two randomized, double-blind, placebo-controlled trials. Patients were split into groups in which they were told to use the drug whilst migraine attack. In the first trial, patients were given ubrogepant in 50mg or 25mg doses or placebo. In the second, the doses were 50mg, 100mg. In both of the trials, an attack and accompanying effects disappearance within the first 2 hours after intake were examined. In the first one, the headache stopped after 2 hours in 21,8% of people using ubrogepant in 50mg dose, 20,7% using 25mg dose and 14,3% in placebo group. Burdensome symptoms recession after 2 hours was reported in 38,9% of 50mg group, 34,1% of 25mg group and 27,4% of placebo group. The most common side effects were nausea and dizziness. In the second trial, the percentage of patients with interrupted headache within 2 hours was 21,2% in 100mg group, 19,2% in 50mg group and 11,8% in placebo group. Accompanying effects interruption was 37,7%, 38,6% and 27,8% respectively. The most frequent side effects were dry mouth, nausea and sleepiness.(18,19) The maximal concentration of ubrogepant in plasma occurs after 1,5 hour from 50mg and 100mg dose intake (high fat meals can slow this process). The drug is metabolized in the liver using CYP3A4 and therefore special precautions must be kept when using CYP3A4 inhibitors such as ketoconazole or verapamil and its inductors like rifampicin. What

is more, ubrogepant should not be used during pregnancy and in patients with severe kidney failure. (20) Importantly, this drug did not affect liver activity and cardiovascular system significantly. (21) In contrary to triptans or ditans, second dose of ubrogepant is effective even in the case of no response in the course of primary treatment. (16)

Rimegepant:

Rimegepant has been approved by the FDA in 2020 in 75mg dose to interrupt acute migraine attack. Safety and effectiveness were proven by randomized, double-blind, placebo controlled third phase trials. (16) In all of them, the participants were split into two separate groups in which they were given 75mg of rimegepant or placebo. The aim of these studies was to evaluate headache and burdensome symptoms interruption within 2 hours from intake. It was validated that headache and symptoms disappeared in bigger group of people after rimegepant intake than in the placebo group. Most frequent adverse effects were nausea and urinary tract infections. (22,23)

A study concerning rimegepant chronic usage in migraine attacks prevention was also conducted. One group received 75mg of rimegepant every second day for 12 weeks and the other was given placebo. A drop of an overall number of days with headache in a month (from 9^{th} to 12^{th} week of the drug administration) in comparison to a 4-week test period without drug usage was evaluated. It was discovered that rimegepant was more effective than placebo and did not cause any severe side effects. (24) A maximal concentration in plasma occurs after 2 hours of oral administration. (2) The drug is metabolized in liver using CYP3A4 and so patients must be very careful while using CYP3A4 inhibitors. (20) This drug, just like ubrogepant or lasmiditan does not cause vasoconstriction and therefore is safe in patients with increased cardiovascular risk. (25)

Atogepant:

Atogepant has received the FDA approval in 2021. In opposition to other drugs from this group, it was examined for the purpose of migraine prevention. (16) Its safety, effectiveness and oral doses range were checked in two different studies.

The first one involved two groups of patients listed in groups using placebo, atogepant in 10mg dose once per day, 30mg once per day, 60mg once per day, 30mg twice per day or 60mg twice per day. A change in days free from migraine during one month period was evaluated. The trial lasted for 12 weeks. In every single group from the five using atogepant, a drop in migraine-free days was observed (compared to placebo group). Most common TEAEs were nausea and tiredness. (26) In the second trial, the patients were split into groups with placebo, 10mg, 30mg or 60mg of atogepant daily for 12 weeks. A drug's effectiveness was proven once again. Most frequent side effects were constipation and nausea. (27)

Zavegepant:

Zavegepant is currently examined as a potential acute migraine attack drug. In opposition to other oral gepants, it was administrated via nose. In the trial, patients were split into placebo, 5mg, 10mg or 20mg of zavegepant groups. A headache and MBS interruption within 2 hours from intake was examined. An effectiveness of 10mg and 20mg doses was found when compared to placebo. The most common side effects were taste disruptions and nasal discomfort. (28)

Conclusion:

Medications presented in this article determine the new pathway in migraine treatment. Their specific characteristics is that none of them causes vasoconstriction. Because of that, they can become helpful for patients with high cardiovascular risk, suffering from vascular diseases such as coronary heart disease or hypertension. These people were so far unable to benefit from available treatment methods (triptans). Drugs listed above stand out for good tolerance, effectiveness and safety. However more research concerning their prolonged usage and its consequences is needed.

Author's contribution

Conceptualization, Aleksandra Kłos, Anna Greguła and Karol Stachyrak; methodology, Mateusz Pawlicki; software, Dawid Mika; check, Aleksandra Kłos and Maciej Lambach; formal analysis, Aleksandra Mazurek and Wiktoria Wilanowska; investigation, Kamila Turek and Wiktoria Wilanowska; resources, Aleksandra Mazurek; data curation, Anna Greguła; writing - rough preparation, Aleksandra Kłos; writing - review and editing, Maciej Lambach, Kamila Turek; visualization, Bartosz Mazur; supervision, Mateusz Pawlicki; project administration, Dawid Mika; receiving funding, Mateusz Pawlicki

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