Treating Menière's Disease with Rimegepant

Stefan C. A. Hegemann, Angela Schell

Abstract

A recent hypothesis states that Ménière's disease (MD) is caused by the inappropriate expression, i.e. enhanced release of the neurotransmitter calcitonin gene-related peptide (CGRP). Here, we tested this hypothesis by administering rimegepant, a new CGRP antagonist approved for the acute treatment of migraine and for the prevention of episodic migraine, to six patients suffering from both MD and migraine. Two patients received the first dose of 75 mg rimegepant to treat an acute attack of MD. One of these two plus the remaining four patients were treated with 75 mg rimegepant every 2nd day for secondary prevention. One patient developed an allergic reaction after the first administration and was excluded from further treatment. In the two patients treated during acute MD, symptoms were relieved and resolved about 30 min earlier than migraine symptoms. While all five patients had reduced migraine, all completely resolved Ménière's symptoms on preventive therapy with rimegepant for up to eight months. These results support the idea that CGRP is linked to the pathogenesis of MD and suggest that inhibition of CGRP signaling may represent a promising therapeutic option for MD patients.

Introduction

Menière's disease (MD) is an inner-ear disorder characterized by attacks of vertigo lasting 20 minutes to 12 hours, accompanied by fluctuating low and mid-frequency hearing loss, increased tinnitus and/or ear pressure. It has an estimated prevalence ranging from 3.5/100,000 in Japan (1) to 513/100'000 adults in southern Finland (2) or between 0.04 and 0.51%, respectively. A recent study in California (3) reported 190/100'000 or 0.19%. The prevalence of MD appears to be lower in Asian countries, although there are few epidemiologic studies. Kim et al. reported that the prevalence of MD in Korea increased from 0.04% in 2013 to 0.15% in 2017(4).

Different prevalences have also been reported for migraine. According to Burch et al. (5), the global prevalence of migraine is 15%, but with variations from 9% in the Western Pacific (China), 12% in the USA, 25-33% in Southeast Asia to 35% in the European Union and Nepal. In a very recent article on the prevalence of migraine in Asia, it was estimated to be 13.8% in Asian countries.

MD and migraine are cross-correlated, with a 10% prevalence of migraine in Korean patients with MD compared with only 3.5% in a matched control group (4). The 3.5% of migraine is much lower than the prevalences mentioned above. Thus, the risk of migraine would be 2.9 times higher in patients with MD than in subjects without MD. Ghavami et al. (6) reported that 51% of MD patients also suffer from migraine. Thus, it is generally accepted that there is a very high correlation between MD and migraine.

It also exists a vestibular migraine, first listed in the 3rd edition of the International Classification of Headache Disorders ICHD-III from 2018 (7). As mentioned in the previous publication on CGRP as the cause of MD, according to Tabet and Saliba (8) "there are no known definitive diagnostic tests that can reliably distinguish the two conditions. Nevertheless, we describe the typical combination of clinical MD symptoms in patients with migraine as two diseases.

Although its first description dates back 163 years (9), the etiology and pathophysiology of MD is still poorly understood and no evidence-based effective oral or intravenous treatment is available. Transtympanic or intratympanic injections of steroids were thought to be promising according to a 2011 Cochrane review (10) that included only one study, but the most recent Cochrane meta-analysis (11) of 10 included trials, all using dexamethasone, concluded that intratympanic corticosteroids

may make little or no difference in the number of people reporting improvement in their vertigo at 6 to 12 months or more of follow-up.
Another, mostly third-step therapy is endolymphatic sac surgery (ESS). However, there is considerable controversy about its efficacy and whether the sac should be decompressed, opened, or shunted (12).
Only destructive procedures such as vestibular neurotomy, neurectomy, labyrinthectomy, or transtympanic injections of aminoglycosides, most commonly gentamicin, have a significant effect on reducing the frequency of vertigo in MD (13). However, these procedures carry a significant risk of hearing loss.
Since all or almost all patients suffering from MD show endolymphatic hydrops (ELH) (14), it is often assumed that MD is caused by ELH. However, guinea pigs with ELH, induced by resection of the endolymphatic sac, do not develop Menière-attacks (15). The only symptom which seemed to be closely correlated to ELH was low frequency hearing loss (16), but this correlation has also been questioned (17).
Various changes occur in the inner ears of MD patients, including signs of inflammation (18) and decreased blood supply (19), and various causes, such as viral (20) or autoimmune inflammation (18) or allergies (21, 22), have been suspected of causing Menière's attacks. Hence MD has recently been called Menière's syndrome, because it is suspected that its symptoms may be due to disparate causes and etiologies. In 1992 Cutrer and Baloh first suspected a common involvement of neuropeptides like “substance P, neurokinin A and CGRP” in MD and migraine (23). They also speculated that “CGRP and possibly other neuropeptides released from trigeminal afferents and vestibular efferents may increase excitability of the inner ear vestibular receptors.”

In 2021 CGRP was suspected to be the main cause for MD (24), because it is one of the main transmitters in cochlear and vestibular efferents, thus explaining simultaneous cochlear and vestibular symptoms. CGRP is a potent vasodilator and ELH may be induced by dilation of capillaries in the stria vascularis, which may induce ELH similar to edema induced in other parts of the body. CGRP is also known to induce neurogenic inflammation (25, 26), explaining the inflammatory signs described in the inner ears of MD patients. Later, MD as well as isolated cochlear or vestibular symptoms were suspected to be caused by inner ear migraine (27). But Frank et al. didn’t focus on CGRP. Since we are still unable to distinguish MD from

vestibular migraine as argued in the hypothesis that CGRP causes MD (24), which is supported to by other authors (6, 27, 28), we also see MD as a special form of an inner ear migraine.

The above suggests that CGRP may be causally involved in MD, and provides a rationale for treating MD with CGRP antagonists, which have been available since 2018. However, the first CGRP antagonists (erenumab, fremanezumab, galcanezumab, eptinezumab) are large monoclonal antibodies that cross the blood-brain barrier (BBB) only by 0.1-0.3% owing to their molecular weight of 180-200 kDa(29). Nevertheless, they work for prevention of migraine because the ganglion of the trigeminal nerve is situated outside the BBB (30). Unfortunately, it has not yet been investigated, whether they may cross the blood-labyrinth barrier (BLB). Although, severe disturbance of the BLB in the cochlea has been reported in older patients with ELH (31).

More recently, small molecular CGRP antagonists, so called gepants, are available. These substances cross the BBB to a limited extent of about 1-3%. The spinal fluid concentrations of telcegepant and olcegepant were only about 1.3% of plasma concentration (32), but Hostetler et al. determined the in vivo cerebrospinal fluid/plasma relation between 2 to 3% and showed the highest level of binding in the cerebellum, brainstem and meninges (33). The 1-3% of plasma level in the CSF measured for gepants are still small, but at least an order of magnitude higher than the 0.1-0.3% reported for galcanezumab (29).The distribution volume in the inner ear is unknown. But even if the gepant molecules would not cross the normal blood-labyrinth barrier, they may still reach the inner ears with severe disturbance of the BLB in MD patients or through the cochlear and vestibular efferents, which arise from the superior olive in the brainstem, where the binding level was high. Nevertheless, we assumed that gepants could reach the inner ear either way and hypothesize that they may prevent Menière-attacks.

Our first goal was to prove in a small pilot study whether treating patients with MD and migraine with gepants would support the hypotheses that 1) MD is caused by CGRP and that 2) gepants can reach the inner ear and prevent MD attacks.

Positive results would support our second goal of organizing a large prospective randomized placebo-controlled clinical trial to test whether this drug will be the first evidence-based effective oral treatment for MD.

Methods

We describe a series of six MD patients who were treated with rimegepant, a new medication for treating migraine. Treatment was in accordance with the Declaration of Helsinki as revised in 2023. An Institutional Review Board approval was not required according to Kantonale Ethik Kommission Zurich (BASEC_Req-2024.00515).
Patients with definite MD according to the 2015 Barany criteria (34) were instructed to fill out a calendar listing all migraine and MD symptoms and their duration. In addition to an intensive history of all MD symptoms audiograms, bilateral bithermal vestibular testing (calorics), video head impulse testing (vHIT) as well as cVEMP, oVEMP, SVV and fundus photography were performed. All anonymized test results will be sent to the interested reader on request. In addition, patients were specifically interviewed about migraine symptoms such as headache severity, duration, and location, as well as associated symptoms such as increased sensitivity to noise and light and aura symptoms. If the patient met the diagnostic criteria of the International Classification of Headache Disorders, 3rd edition (ICHD-III), a diagnosis of migraine was made (35). If both diagnoses were confirmed, they were asked to participate in this pilot study. All patients were also asked about previous treatments/medications to prevent migraine and/or MD attacks and their effects.

We first wanted to treat patients with both MD and migraine to avoid off-label therapy. We enrolled six patients with the following history of MD, at least 3 Menière-attacks per month in the last 6 months and rotatory vertigo of at least 3 hours in most Menière-attacks during the last 6 months.
When we saw the very impressive effect in the first four patients, we decided to also try the same medication in one patient with MD only. Two patients were instructed to start their preventive medication at the beginning of their next Ménière's attack to see if there was also an acute effect on the duration of Ménière's symptoms.

Results

Six patients agreed to take part in this pilot study. Five suffered from migraine and MD and one (no 6) suffered from migraine between about her 20th and 60th and from MD since her 74th year of life. Table 1 shows their characteristics.

Table 1: Characteristics of patients included into study.

Pat. No	Gender	Age at inclusion into study	Age at onset /end of Migraine	Age at onset of MD
1	Female	76 ys	67 ys	65 ys
2	Female	57 ys	25ys	51 ys
3	Female	45 ys	17ys	39 ys
4	Male	43 ys	16 ys	34 ys
5	Male	62 ys	41 ys	41 ys
6	Female	82 ys	20/60ys	74 ys

As expected, in all five patients treated with rimegepant (Vydura) every second day, the frequency of migraine attacks was significantly reduced after the first dose of rimegepant. In addition, all five patients have been free of Menière's attacks since their first dose of rimegepant. After five months, one of them (patient #2) was unable to continue the rimegepant regimen due to a shortage of supply. During the 3 weeks without rimegepant, she had 8 migraine attacks and 6 MD attacks. Since restocking, she had no more attacks of migraine and no more attacks of MD. Because of this three-week break, only one of the five patients was free of MD attacks for more than 8 months, one had only a break of attack-free period for 3 weeks and most likely would also be free of MD attacks for 8 months. Patient no. 3 is free of MD attacks for 7 months, patient no. 5 for more than 6 months and patient no. 6 for more than 4 or almost 5 months. Table 2 shows the duration of freedom from MD attacks and other descriptive data.

One patient (#4 in Tab.1) developed severe skin rush on the whole body as well as pain in the right upper abdomen and diarrhea. The medication was immediately stopped.

Tabel 2: List of patients and their estimated frequence of attacks (EFA) of MD or migraine and their reduction since intake of rimegepant (RG) up to the time of last control.

Pat. No	EFA of MD (6 month ahead)	EFA of Migraine (6 month ahead)	First RG intake (date)	Duration of RG intake (months)	No. of MD attacks under RG	No. of Migraine attacks under RG	Previous treatments without success
1	10-12	6-12	2023-11-08	>8	0	3	BH, ST, IST
2	12-14	12-22	2023-11-12 (paused from 2024-4-12 to 2024-05-03)	>8	0	3	BH, ST, ITS, TM, Mg^{++}, Emab, MP,
3	7-9	8-9	2023-12-15	>7	0	2	BH, ITS, MP, Emab
4	12-16	12-16	2024-01-05	1 tablet once	12-16, **no RG**	12-16, **no RG**	BH, $Mg^{++,}$ B2, ITS , Emab, Fmab
5	8-10	10-20	2024-02-02	>6	0	0	BH, Mg^{++}, B2, ITS, ST
6	12-15	no migraine since 22 years	2024-03-12	>4	0	0	BH, ITS, Mirtazapine

Abbreviations for previous treatments: Betahistine: BH, Erenumab: Emab, Fremanezumab: Fmab, IT-steroids: ITS, Magnesium Mg^{++}, Metoprolol MP; Riboflavin: B2, Sumatriptan: ST, Topiramat: TM.
The pause of RG intake in patient #2 was due to shortage of supply.

Patient no. 4 took the first dose of rimegepant at the start of a Menière attack with simultaneous migraine. Although he showed the described allergic symptoms, his Menière symptoms usually lasting for 6-12 hours started to improve after about one hour and were completely resolved at 1.5 hours. Interestingly, his migraine symptoms also improved, but about half an hour later than his Menière symptoms.

Table 3: report of patient #4 (according to tab.1) with effects of Rimegepant on symptoms during an attack of MD and Migraine.

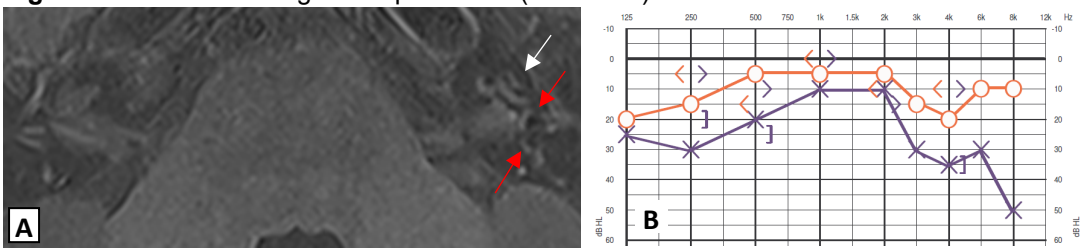
Patient #4	**Date of migraine/MD-attack: 2024-01-05**					
Symptom	**Stength (0-10)**	**Affected ear (right/ left/both)**	**Start of symptom (time)**	**Intake of rimege-pant (time)**	**Start of symptom reduction (time)**	**Symptom resolved (time)**
Tinnitus	9-10	right	15:45	**15:50**	16:40	18:30
Pressure feeling	7	right	15:50		16:40	17:30
Hearing loss	9-10	right	15:50		16:40	17:30
Rotatory vertigo	8		15:50		16:40	17:30
Headache	8		15:50		17:30	18:00
Noise sensitivity	8	both	15:50		17:30	18:00
Light sensitivity	8		15:50		17:30	18:00

Table 4: report of patient #5 (according to tab.1) with effects of Rimegepant on symptoms during an attack of MD and Migraine.

Patient #5	Date of migraine/MD-attack: 2024-02-02					
Symptom	**Stength (0-10)**	**Affected ear (right/ left/both)**	**Start of symptom (time)**	**Intake of rimege-pant (time)**	**Start of symptom reduction (time)**	**Symptom resolved (time)**
Tinnitus	7	left	9:39	**9:53**	10:30	11:00
Pressure feeling	5	pulse for about 1s	9:39			9:39
Hearing loss	?	left	9:39		10:30	11:00
Rotatory vertigo	5		9:39		10:30	11:00
Headache	4		9:39		sleep at 13:30	15:40
Noise sensitivity		both	9:39			15:30
Light sensitivity	4		9:39			15:30

Patient no. 5 also took the first dose 14 minutes after the start of Menière symptoms as well as migrainous symptoms (see tab.2). While his attacks of spinning vertigo were usually lasting 3-6 hours with increased tinnitus and hearing loss usually lasting much longer than vertigo, he used sumatriptan spray before to reduce his symptoms. This reduced the duration of symptoms, especially of vertigo to 30-60 minutes. 37 minutes after he took rimegepant all Menière-symptoms started to improve and were completely resolved after 1 hour.

Figure 1: MRI and audiogram of patient #4 (Tab. 1 &2)



A) MRI 3D inversion recovery sequence showing cochlear (white arrow) and vestibular (red arrows) endolymphatic hydrops Grade 1 in the left ear, according to Baráth et al. (36). B) Audiogram 5 years after start of MD showing low and high frequency hearing loss called “peak.audigram”.

In both patients migrainous headache with increased light- and noise-sensitivity lasted longer than the MD-symptoms. Patient no 5 became tired and had a sleep for two hours. After this nap, his migrainous symptoms (headache as well as increased sensitivity to noise and light) were also completely resolved.

Discussion

We describe a small case series of six MD patients who were treated with rimegepant. We saw an impressive positive effect of rimegepant on acute MD-attacks

in two patients, who took the first dose shortly after the combined onset of migraine and MD symptoms and whose MD symptoms improved even earlier than the migraine symptoms.
We also saw a promising preventative effect in all six patients of our small first case series. Five of these patients used it as a preventative treatment for both migraine and MD and patient no. 6 used it for prevention of MD only, because her last migraine attack was about 14 years before her first Menière attack. The effect in migraine has already been described (37, 38), but we describe very promising effect of rimegepant in both acute MD-attacks and the prevention of MD. Especially remarkable seems that migraine symptoms were significantly reduced, but MD-symptoms were completely abolished in all five patients during the preventive period, which is still going on. And even when treating an acute attack, MD symptoms improved better and faster than migraine symptoms.

This study has several limitations. First, the study sample is quite small. We know that such a small case series has a very week evidence and doesn't prove the effect statistically. Nevertheless, this study wasn't designed to provide statistical evidence, but as a pilot study to see if this new medication is worth developing a larger randomized controlled trial (RCT). Therefore, one author (SH) tried to start prevention during an acute attack in two patients with prolonged vertigo to see if an acute effect could be observed and then included in a larger study. However, all participants in the study were well characterized both clinically and with audio-vestibular function tests.
Despite these limitations, we believe that this small case series may be of interest to clinicians who are managing this disabling condition and have no evidence-based non-destructive medical therapy available
Therefore, we decided to publish these very promising first results in a very small group of patients which support the previous hypothesis that MD is mainly caused by CGRP (24) at least in patients with MD and migraine and possibly also in patients with MD only. The efficacy in only one patient with MD only is even less evident than in the four with MD and migraine, but it shows at least a possible effect. Since other authors also argue for an inner ear migraine (6, 27, 39, 40), we agree with this concept and think that a therapy directed at a specific molecule that shows an effect in a pilot study is a strong support to initiate a large RCT.

With regard to the one patient from our small case series we also suggest that rimegepant may have a significant preventive effect not only in patients with MD and migraine, but also in patients with MD only. This will be an important question in the planned RCT.
As described in the introduction, there are no evidence-based therapies described for the treatment of an acute attack of MD, and all preventive treatments for MD - except vestibular destructive procedures - are controversial, so there are no generally accepted medications for the treatment of MD.

Conclusion

Despite the mentioned limitations of this very small case series and according to our hypothesis, we would suggest to treat patients with MD and migraine as well as isolated MD but without migraine with rimegepant or other gepants, if they are available. We suggest that rimegepant is a potentially strong medication for prevention of MD as well as for treating acute MD attacks.
A larger, double-blind, randomized, placebo-controlled trial is warranted and is about to be initiated to provide scientific evidence of this impressive effect of rimegepant. We will also evaluate the effect of rimegepant on hearing tests, vestibular function tests and endolymphatic hydrops. We hope that we will soon have scientific proof that the hypothesis that CGRP causes MD is correct and that this disabling disease can be effectively treated, significantly improving the quality of life of MD patients. We are pleasantly surprised that rimegepant appears to be even better at preventing MD than migraine, for which it was originally developed. And the faster and better effect in acute attacks of Meniere's disease is also very interesting and promising.

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