COMBINATIONS OF NEW MIGRAINE THERAPIES –

PROS & CONS

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Disclosures: Talks/Advisory boards/Consultant for

AbbVie, Eli Lilly, Lundbeck, Novartis, Pfizer, Teva, Roche

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AGENDA

- First, I will discuss the combination use of onabotulinumtoxinA and CGRP monoclonal antibodies
- Secondly, I will discuss the combination therapy with CGRP monoclonal antibodies and gepants
- I will take you through some of the pros and cons of these combination therapies

COMBINATION THERAPY

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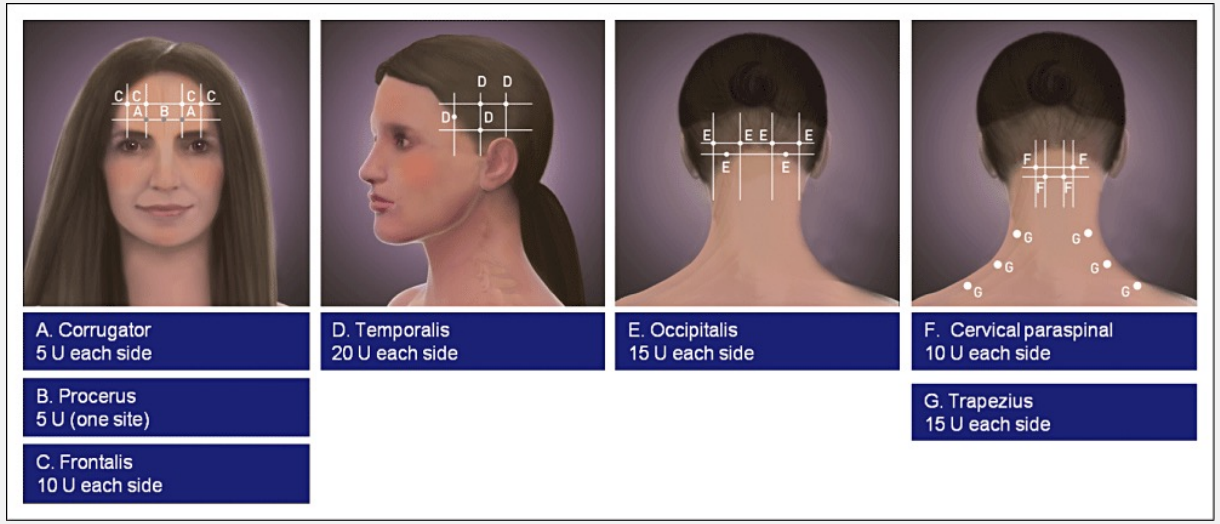
- Onabotuliniumtoxin A (Botox)



- CGRP monoclonal antibodies (mAbs)

- CGRP receptor blockers (gepants)

«DIFFICULT TO TREAT» PATIENTS

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- Proposed definitions EHF
- Resistant migraine — failed at least 3 profylactic medications

- Refractory migraine — failed all of the profylactic medications
- Debilitating migraine — failed at least 2 triptans

Sacco S, Braschinsky M, Ducros A, Lampl C, Little P, van den Brink AM, Pozo-Rosich P, Reuter U, de la Torre ER, Sanchez Del Rio M, Sinclair AJ, Katsarava Z, Martelletti P. European headache federation consensus on the definition of resistant and refractory migraine : Developed with the endorsement of the European Migraine & Headache Alliance (EMHA). J Headache Pain. 2020 Jun 16;21(1):76. doi: 10.1186/s10194-020-01130-5. PMID: 32546227; PMCID: PMC7296705.

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NO CONSENSUS

- No global consensus in how to handle previously used migraine profylactic medication when initiating newer therapies

- National guidelines
- European guidelines
- Reimbursement policies
- What other doctors do

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COMBINATION USE OF BOTOX AND CGRP MABS

Suitable for severe chronic migraine:

- This combination is often recommended for individuals with severe chronic migraine, who have not responded adequately to single therapy with one of these

PROS

Bridging:

- Botox injections are typically administered every 12 weeks, and the CGRP mAbs typically every month

- This can help maintain migraine prevention throughout the treatment cycle even in the “wear out” periods, “bridging” the gaps

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PROS

Enhanced Efficacy:

- CGRP mAbs and Botox work through different mechanisms preventing migraine attacks

- CGRP mAbs target the calcitonin gene-related peptide or its receptor, which is associated with migraine pain, while Botox inhibits the release of neurotransmitters involved in pain transmission

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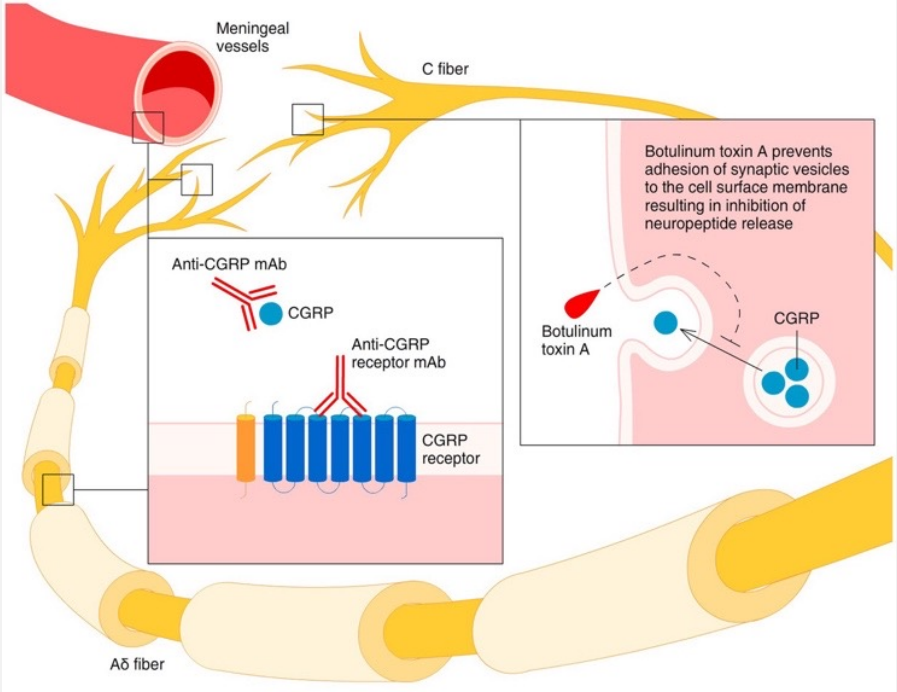
PROPOSED MECHANISMS FOR THE SYNERGIC ACTIVITY



Proposed mechanisms for the synergic activity of anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs) and botulinum toxin A in the prevention of migraine with a focus on the CGRP signaling pathway

Ashina, M., et al., *Migraine: epidemiology and systems of care.* Lancet, 2021. **397**(10283): p. 1485-1495.

MIGRAINE TREATMENT TARGET: CGRP

Triptans & ergots prevent CGRP release

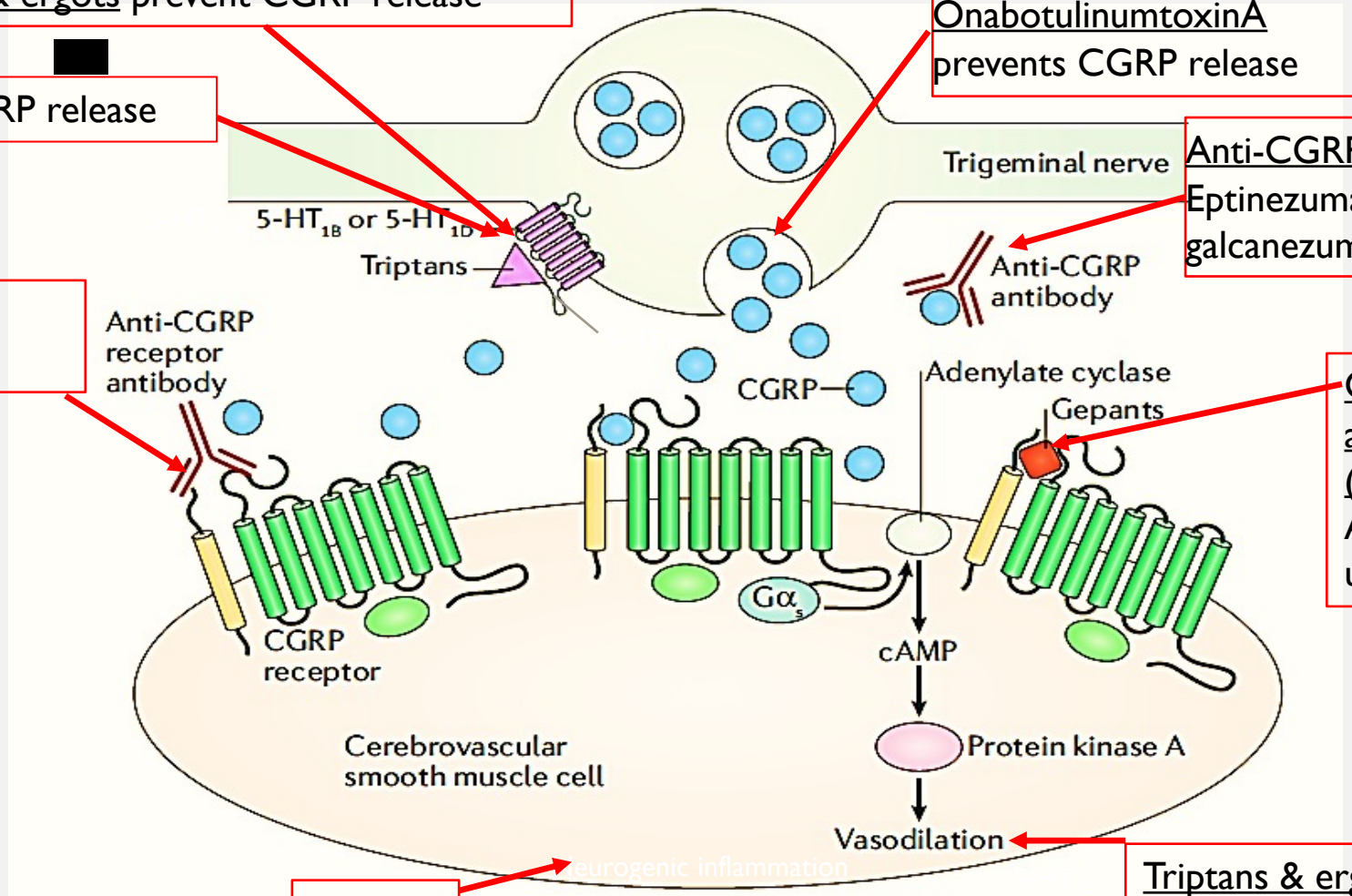
Lasmiditan prevents CGRP release

OnabotulinumtoxinA prevents CGRP release

Anti-CGRP ligand mAbs: Eptinezumab, fremanezumab, galcanezumab

Anti-CGRP receptor mAb: Erenumab

CGRP receptor antagonists (gepants) Atogepant, rimegepant, ubrogepant*, zavegepant*



*Not approved in the EU

NSAIDs

Triptans & ergots constrict CGRP-dilated vessels

Adapted from Edvinsson L, Haanes KA, Warfvinge K, Krause DN. CGRP as the target of new migraine therapies - successful translation from bench to clinic. Nat Rev Neurol. 2018 Jun;14(6):338-350.

PROS

Minimal Drug Interactions:

Since CGRP mAbs and Botox may work through different mechanisms, there are generally no significant drug interactions or contraindications between the two treatments

PROS

Well-Tolerated:

- Both CGRP mAbs and Botox are generally well-tolerated with relatively few side effects compared to the traditional oral migraine preventatives

CONS

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Cost:

- The direct cost of CGRP mAbs and Botox are both still regarded high
- A barrier to access this combination for some countries due to reimbursement rules
- Can lead to further social inequalities

CONS

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Regular Injections:

- CGRP mAbs are typically administered monthly or quarterly, while Botox is administered every 12 weeks
- The combination therapy involves multiple injections and/or even IV infusion at the hospital
- Increasing the waiting lists at the hospitals and logistical issues

REAL-WORLD STUDIES

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- The combination use of Botox and CGRP mAbs may be considered, especially when one of these migraine treatments alone have proven to be less effective

- In real-world studies, this combination treatment approach has shown to be well tolerated, with no new safety signals identified, and in some studies associated with additional clinically meaningful benefits

- In a real-world study *, 45.1% of patients had clinically meaningful improvement in migraine-related disability (≥ 5-point reduction in MIDAS score) after ~ 6 months

*Blumenfeld AM, Frishberg BM, Schim JD, Iannone A, Schneider G, Yedigarova L, Manack Adams A. Real-World Evidence for Control of Chronic Migraine Patients Receiving CGRP Monoclonal Antibody Therapy Added to OnabotulinumtoxinA: A Retrospective Chart Review. Pain Ther. 2021 Dec;10(2):809-826. doi: 10.1007/s40122-021-00264-x. Epub 2021 Apr 21. PMID: 33880725; PMCID: PMC8586140.

RETROSPECTIVE CHART REVIEW

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- A retrospective chart review comparing CM patients treated with erenumab alone (n= 70) or as an add on to Botox (n=73)
- The reduction in MHD was less with the dual therapy
- The probability to achieve a ≥ 50% reduction in MHDs was lower with the dual therapy – odds ratio 0,57

Jaimes A, Gómez A, Pajares O, Rodríguez-Vico J (2023) Dual therapy with Erenumab and onabotulinumtoxinA: no synergistic effect in chronic migraine: a retrospective cohort study. Pain Pract Apr 23(4):349–358. https://doi.org/10.1111/papr.13196

CONS

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Limited Data on Long-Term Safety:

- While both CGRP mAbs and Botox have shown promise in reducing the frequency of migraines in some real world studies, there is limited long-term data on the safety and efficacy of using them in combination

- More research is needed to establish the long-term benefits and potential risks of this approach

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COMBINATION OF CGRP MABS AND GEPANTS

- CGRP ligand binding mAbs and gepants target distinct components within the CGRP pathway. This dual approach can potentially enhance symptom relief for certain individuals.
- Combination therapy with CGRP antibodies for prevention and gepants for acute treatment could be a potential strategy to manage severe migraine headache
- No data on effect or safety on long term combination of CGRP mAbs and prophylactically use of Gepants

PROS

- Can be used to bridge between mAbs injections for patients who are experiencing «wear out» effect

- Patients who are still having more than 8-10 migraine days per month in spite of CGRP mAbs treatment may benefit from Gepants for treating attacks in order to avoid MOH overusing triptans or OTC medications

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CONS

There is limited data on the safety and efficacy of using the mAbs and gepants in combination. More research is needed to establish the long-term benefits and potential risks of this approach

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EHF GUIDELINES

2018

EM: discontinuing oral profylactic before starting mAbs

CM: add on mAbs to oral profylactic, reconsider the oral

Discontinue Botox injections before starting mAbs if Botox had provided an inadequate response

2022

Combined use is optional, left to individual consideration

CONCLUSION

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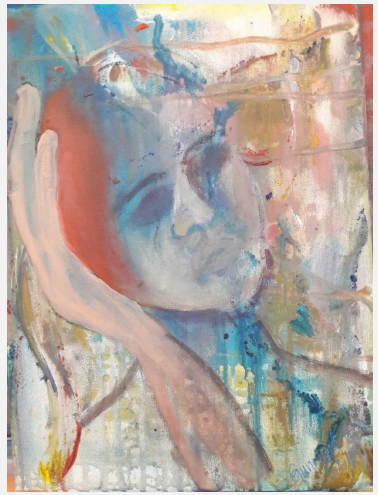
- Aim for individual treatment to achieve an optimal outcome
- The decision should be made on a case-by-case basis, taking into account the potential benefits and risks of the treatment
- RCT s are highly needed



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- One extraslide:

COMBINATION OF BOTOX AND GEPANTS

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Prospective, observational study

- This analysis included 122 participants who treated 599 attacks with ubrogepant* while on onabotulinumtoxinA
- 84.2% were triptan insufficient responders
- After 30 days of real-world use of ubrogepant* with onabotulinumtoxinA 77.6% met the criteria for optimized treatment

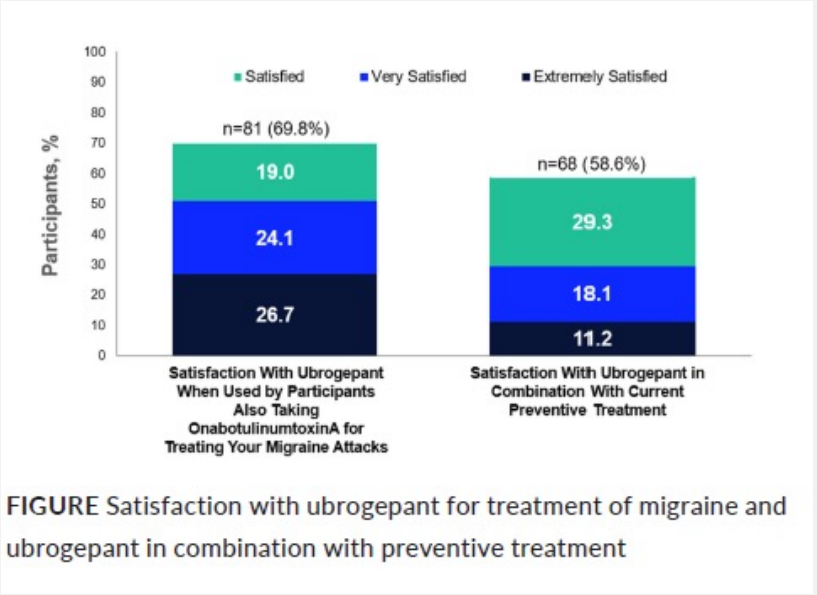

FIGURE Satisfaction with ubrogepant for treatment of migraine and ubrogepant in combination with preventive treatment

*Not approved in the EU

Hutchinson, Engstrom, Serrano, Davis, Sommer, Contreras-De Lama, Lipton
Headache, The Journal of Head and Face Pain, Volume 61,2021, Pages1-186