Neurologybytes

CONy 2019

APRIL 4-7, 2019
MADRID, SPAIN

CONGRESS HIGHLIGHTS
MAGAZINE

CONGRESS HIGHLIGHTS
MAGAZINE

Are Anti-CGRP mAbs Future First-Line Agents in Migraine and Cluster Headache?

The first debate, hosted by Dr. Christian Lampl (Headache Medical Centre Linz, Austria), explored the question whether monoclonal antibodies (mAbs) to calcitonin gene-related peptide (CGRP) will become first-line treatment not only for migraine, but also for episodic cluster headache.

Go to this artice - page 7

APRIL 4-7, 2019
MADRID, SPAIN

6 April 2019
Migraine Sessions
at CONy 2019

CBT and Biofeedback Training in Migraine Prophylaxis – Yea or Nay?

This year's CONy featured intriguing debates on alternative modes of treatment for migraine—an extremely debilitating disorder affecting 1 in 10 individuals globally.[1] With several new prophylactic treatments currently available, opportunities are emerging for easing the burden of suffering in patients with migraine.

In a session hosted by Dr. Robert E. Shapiro (University of Vermont, VT, USA), migraine experts Drs. Steven M. Baskin (New England Institute for Neurology and Headache, Stamford, CT, USA) and Mark Braschinsky (Tartu University Hospital, Headache Clinic, Estonia) debated whether cognitive behavioral therapy (CBT) and biofeedback training can be as effective as medication in the prophylactic treatment of migraine.

Representing the view that preventive pharmacotherapy can be replaced by psychological interventions in certain patients, Dr. Baskin argued that psychological intervention can train the individual to manage stress and other headache triggers, as well as promoting wellness activities and healthy sleeping habits. Dr. Baskin cited the expert opinions of well-renowned migraine specialists Drs. Dimos Mitsikostas and Alan Rapoport that the current standard preventive treatments for migraine were fraught with challenges, such as lack of efficacy in a large number of patients, tolerability and safety issues, and non-compliance.2 In this context, and backed by recent clinical evidence, Dr. Baskin posited that CBT and biofeedback training constitute a set of safer, more cost-effective, and complementary approaches that could have a significant impact on patients' quality of life.

Taking the opposing view, Dr. Braschinsky reviewed recent clinical data that did not show clear evidence of clinical efficacy of non-pharmacologic interventions. According to Dr. Braschinsky, clinical trials to date suffer from fundamental methodological flaws, which render their findings unreliable. Such limitations include poorly defined inclusion criteria, small number of patients, and unclear intervention. Therefore, Dr. Braschinsky concluded that CBT and biofeedback training do not currently have convincing data on disability, number of headache days, and number of headache attacks.

At the end of the debate, while the audience was evenly split between the 2 opposing positions, Drs. Braschinsky and Baskin both agreed that standardized protocols are needed in order to obtain more robust data in this area.
.

References

1. GBD 2015 Disease and Injury Incidence and Prevalence Col laborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis of the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1545-602.

2. Mitsikostas DD, Rapoport AM. New players in the preventive treatment of migraine. BMC Med. 2015;13:279. doi: 10.1186/s12916-015-0522-1.

6 April 2019
Migraine Sessions
at CONy 2019

Does the Blood–Brain Barrier Open During a Migraine Attack?

Another intriguing session at CONy 2019 featured a debate on whether the blood–brain barrier (BBB) transiently opens during migraine attacks. Although inflammation and BBB disruption are important contributors to many neurologic disorders, and inflammation has been linked to migraine pathogenesis, it is still unclear whether BBB integrity is disrupted during migraine attacks.

In the session chaired by Dr. José Miguel Laínez (Universidad Católica de Valencia, Spain), Dr. Pablo Irimia Sieria (Clínica Universidad de Navarra, Pamplona, Spain) discussed evidence for BBB disruption as a result of cortical spreading depression (CSD)—an intense wave of neurologic depolarization. CSD is considered to be associated particularly in migraine with aura, and could lead to BBB leakage through disturbance of cerebrovascular reflexes. Dr. Irimia discussed several animal studies, which have shown that CSD can induce transient BBB leakage and associated brain edema 3–6 h after experimental CSD induction. The BBB leakage appears to be transient, recovering approximately 48 h after experimental CSD induction. According to Dr. Irimia, there is strong evidence in favor of BBB disruption during migraine attacks, particularly in migraine with aura.

Prof. Messoud Ashina (Rigshospitalet Glostrup, Copenhagen, Denmark) took the opposing view, stating that there is no evidence for BBB disruption during migraine attacks in humans, and noting that many patients report aura symptoms without headache. He quoted a recent study by Hougaard et al.1 that used contrast-enhanced high-field MRI to investigate BBB permeability and tissue perfusion in migraineurs with and without aura during migraine attacks. There was evidence of increased perfusion in parts of the brain during the phase of migraine with aura, but no evidence of BBB disruption during any phase of migraine, with or without aura. He further emphasized that studies in humans so far have all failed to show a correlation between BBB disruption and migraine.

At the end of the debate, the audience leaned 2:1 towards the position defended by Prof. Ashina, which was that the BBB did not open during a migraine attack. The jury is clearly still out on whether there is a correlation between inflammation, BBB disruption and migraines with and without aura. If there is a correlation between BBB leakage and migraine—and it is currently not possible to detect it due to technical challenges associated with studying this in humans—the next question is whether it is clinically relevant. Uncovering the potential role of BBB leakage in migraine is also extremely important with respect to improving migraine treatments, because transient BBB opening would present opportunities to target the CNS directly with molecules too large to cross an intact BBB.

References

1. Hougaard A, Amin FM, Christensen CE, et al. Increased brainstem perfusion, but no blood-brain barrier disruption, during attacks of migraine with aura. Brain. 2017;140(6):1633-42.

6 April 2019
Migraine Sessions
at CONy 2019

Are Anti-CGRP mAbs Future First-Line Agents in Migraine and Cluster Headache?

Continuing our coverage of CONy 2019, we are reporting on two debates supported by Teva in the field of diagnosis and treatment of migraine.

The first debate, hosted by Dr. Christian Lampl (Headache Medical Centre Linz, Austria), explored the question whether monoclonal antibodies (mAbs) to calcitonin gene-related peptide (CGRP) will become first-line treatment not only for migraine, but also for episodic cluster headache. Dr. Lars Edvinsson (Lund University Hospital, Sweden)—who discovered CGRP and established its link to the trigeminovascular system implicated in migraine in the early 1980's—supported the view that anti-CGRP mAbs had the potential to become first-line agents in the treatment of both of these headache types. Dr. Edvinsson emphasized the fact that most traditional prophylactic drugs—e.g. beta-blockers, anti-depressants, anti-epileptics, and botulinum toxin—were originally developed for other indications. As a result of their lack of specificity to migraine, their use is often accompanied by adverse events that lead to poor patient compliance beyond 1 year.1 In contrast, Dr. Edvinsson presented anti-CGRP mAbs as agents specifically designed to target the migraine pain pathways. The favorable safety and tolerability of this drug class also offers the hope of improved patient compliance.

In the other corner, Dr. José Miguel Laínez (Universidad Católica de Valencia, Spain) argued that failure of traditional preventive treatments for migraine and cluster headache often results from lack of optimization of the treatment regimens. In this context, Dr. Laínez expressed that anti-CGRP mAbs would unlikely become first-line agents in these indications as long as current cost-effective agents are not used as part as individualized regimens to increase patient compliance. From a clinical evidence point of view, Dr. Laínez presented studies that showed similar benefits with anti-CGRP mAbs vs. traditional preventive agents in episodic migraine.2 In chronic migraine, anti-CGRPs failed to demonstrate superiority vs. topiramate or botulinum toxin.3 At the end of the debate, the audience leaned towards Dr. Laínez' skepticism, but both sides agreed that the place of anti-CGRP mAbs in the treatment algorithm will be determined as more clinical evidence is produced in larger, longer-term randomized controlled trials.

References

1. Hepp Z, Dodick DW, Varon SF, Gillard P, Hansen RN, Devine EB. Adherence to oral migraine-preventive medications among patients with chronic migraine. Cephalalgia. 2015;35(6):478-88.

2. Hou M, Xing H, Cai Y, Li B, Wang X, Li P, Hu X, Chen J. The effect and safety of monoclonal antibodies to calcitonin gene-related peptide and its receptor on migraine: a systematic review and meta-analysis. J Headache Pain. 2017;18(1):42. doi: 10.1186/s10194-017-0750-1.

3. Dodick DW, Turkel CC, DeGryse RE, et al. Assessing clinically meaningful treatment effects in controlled trials: chronic migraine as an example. J Pain. 2015;16(2):164-75.

6 April 2019
Migraine Sessions
at CONy 2019

Are Migraine With Aura and Without Aura the Same Disease?

As part of our CONy 2019 highlight series, the second of two Teva-supported debates revealed fascinating insights into the importance of aura as a prodrome of migraine.

The debate hosted by Dr. Dimos Mitsikostas (National & Kapodistrian University of Athens, Greece), opposed Drs. Isabel Pavão Martins (University of Lisbon, Portugal) and Margarita Sánchez del Río (Clínica Universidad de Navarra, Madrid, Spain), and examined whether migraine with aura (MA) and migraine without aura (MoA) are the same disease. Dr. Mitsikostas opened the session by reminding the audience that 1–2 out of 5 patients with migraine have auras and that this prevalence is identical in both genders.1 He further described that the likely basis of migraine aura symptoms lies in the phenomenon of cortical spreading depression (CSD), a wave of increased electrocortical activity and vasodilation (hyper-perfusion), followed by sustained decreased activity and prolonged vasoconstriction (hypo-perfusion).[2]

As a proponent of the position that MA and MoA are the same disease, Dr. Martins argued that human neuroimaging studies have shown that CSD play a role in migraine, regardless of the presence of aura. She also presented findings of a study by Vincent MB and Hadjikhani N[3] that would suggest that MoA could simply be a migraine with subclinical aura. Dr. Martins further provided evidence of the presence of transient visual disturbances (TVD) during migraine attacks in patients with MoA.[4] As a last argument in support of her position, Dr. Martins also reminded the audience that most prophylactic agents improve patients with migraine regardless of the presence of aura.

On the other side of the debate, Dr. Sánchez del Río presented her case for a clear distinction between MA and MoA. She even proposed to reclassify MA as "headache attributed to aura." In support of her position, Dr. Sánchez del Río emphasized differences between MA and MoA in terms of: clinical aspects (e.g. aura sometimes occurs without headaches); treatment (MA not responsive to acute or preventive drugs used in MoA); pathophysiology (e.g. CGRP triggers MoA but not MA); and cardiovascular risk (increased in MA).[5-6]

At the end of the debate, the audience voted with a narrow majority that MA and MoA were manifestations of the same disease. The questions from the audience and rebuttals from the debaters left us with one certainty: this debate is far from over.

References

1. Stewart WF, Lipton RB, Dowson AJ, Sawyer J. Development and testing of the Migraine Disability Assessment (MIDAS) Questionnaire to assess headache-related disability. Neurology. 2001;56(6 Suppl 1):S20-8.

2. Hadjikhani N, Sanchez Del Rio M, Wu O, et al. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. Proc Natl Acad Sci USA. 2001;98(8):4687-92.

3. Vincent MB, Hadjikhani N. Migraine aura and related phenomena: beyond scotomata and scintillations. Cephalalgia. 2007;27(12):1368-77.

4. Mattsson P, Lundberg PO. Characteristics and prevalence of transient visual disturbances indicative of migraine visual aura. Cephalgia. 1999;19(5):479-84.

5. Pascual J, Caminero AB, Mateos V, et al. Preventing disturbing migraine aura with lamotrigine: an open study. Headache. 2004;44(10):1024-8.

6. Vgontzas A, Burch R. Episodic migraine with and without aura: key differences and implications for pathophysiology, management, and assessing risks. Curr Pain Headache Rep. 2018;22(12):78. doi: 10.1007/s11916-018-0735-z.

5 April 2019
MS Sessions
at CONy 2019

Current Controversies in MS

For the 13th consecutive time, this year's World Congress on Controversies in Neurology (CONy 2019, held in Madrid, Spain on April 4–7, 2019) covered a range of current, intriguing topics in the field of Multiple Sclerosis (MS).

Friday's MS sessions opened with a thorough examination of neurofilaments as viable biomarkers of MS progression, as well as their potential to replace magnetic resonance imagining (MRI) as a monitoring tool. Due to her opponent not being present for the debate, Dr. Georgina Arrambide from the Center of Multiple Sclerosis of Catalonia (Cemcat) had the daunting task of representing both sides of the argument as a pro-NfL advocate herself.

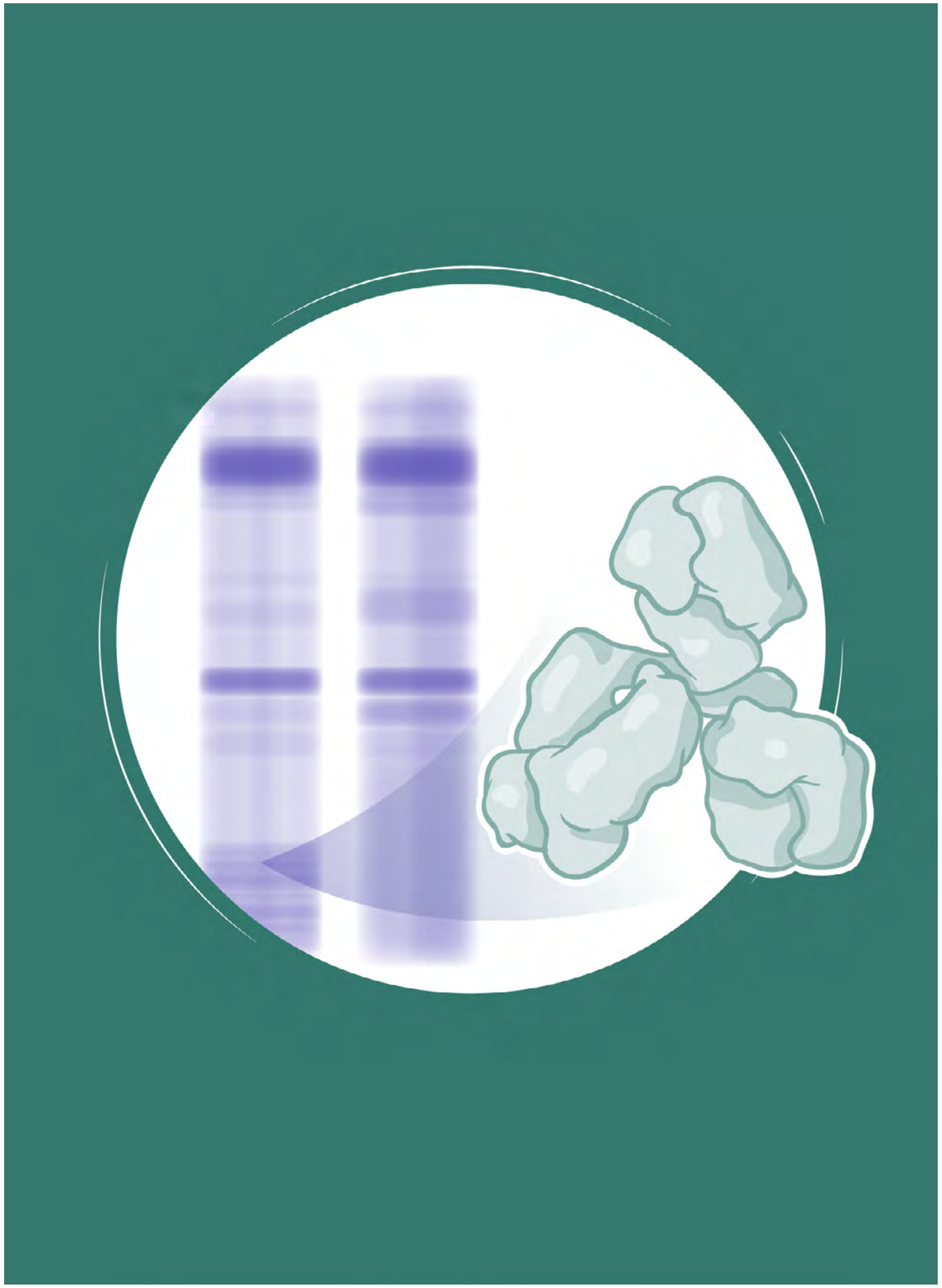
Neurofilament light chain (NfL) is released in the cerebrospinal fluid (CSF) after axonal injury leading to higher blood and CSF levels in patients with MS—and other neurological diseases—than in healthy subjects. Increased levels have been shown to correlate with MRI lesions and other measures of disease activity. Measurement of NfL serum levels, however, is fraught with reproducibility and validation challenges that render its widespread adoption difficult at this point in time. The audience in attendance was in strong agreement with this observation and overwhelmingly voted that they did not see NfL serum levels as replacing MRI anytime soon as the gold standard for monitoring MS progression.

In stark contrast, the next panel debated the continued value of evoked potentials (EPs) in the diagnosis and monitoring of MS. These painless, non-invasive, cost effective, and quick clinical tests—first proposed by Dr. Charles M. Poser in 1986 in the context of MS diagnosis—have been progressively losing steam as more emphasis was being put on MRI. The broad acceptance of the McDonald's criteria in 2001—which elevated MRI to the gold standard in MS diagnosis—have rendered EPs obsolete in the eyes of a broad section of the MS community. Dr. Letizia Leocani from the University Hospital San Raffaele in Milan, however, reminded the audience that "old" doesn't necessarily mean obsolete. As an illustrative example, Dr. Leocani noted that reflex hammers have been used since the 19th century and are still relevant today in neurological examination. She also pointed to recent research that indicates that EPs are more sensitive than MRI to early brainstem damage and for the prediction of long-term disability levels. On the other side of the debate, Dr. Bianca Weinstock-Guttman from the University of Buffalo, New York, expressed concerns about the validation and reproducibility of EP testing. She noted that EP metrics are indeed sensitive to external factors such as temperature and medications. Additionally, EPs have shown to be poor indicators of cognitive and cerebellar dysfunctions, thus decreasing their value as a diagnostic and monitoring tool. The audience in attendance eventually sided with Dr. Weinstock-Guttman's anti-EP argument in a 2:1 ratio. It appears that we may have entered a post-EP world, but ongoing research by Dr. Leocani could indicate that the fight is far from over. We will be monitoring the progress of the EP debate with great attention in anticipation of next year's CONy conference!

5 April 2019
MS Sessions
at CONy 2019

Controversies in MS Treatment and Monitoring

One of the discussions at this year's CONy is the safety of, and justification for, the use of biosimilars over brand-name drugs in Multiple Sclerosis (MS). This very topic had already been the source of debate at CONy 2015 in Budapest[1] and this Friday afternoon in Madrid, it made a come-back in an interesting session hosted again by Dr. Ron Milo from the Barzilai Medical Center in Ashkelon, Israel.



The topic of biosimilars is timely in the field of MS with drug patents starting to expire and generics entering the market. Dr. Milo started the session by defining the terms "generic" and "biosimilar" as they apply to fully characterized small molecules (<5 kD) and partially characterized biologics (5–150 kD), respectively. While generic drugs only require demonstration of bioequivalence, biosimilars may need further pharmacodynamic (PD) and/or clinical studies to establish similarities to the brand-name biologic. In Dr. Milo's opinion, the case of difficult-to-characterize

non-biologic complex drugs (NBCDs), such as glatiramer acetate (GA) showcases the limitations of the 2 approaches described above. Using any other manufacturing process than that of the original NBCD will undoubtedly lead to a significantly different chemical entity. As a result, according to Dr. Milo, such a drug would have to meet its own complete and distinct regulatory approval requirements.

Dr. Ovidiu Bajeranu from the University of Medicine and Pharmacy "Carol Davila" in Bucharest, Romania, presented a case in favor of using biosimilars in MS for the high cost-savings that they could offer with similar clinical efficacy. He warned, however, that follow-on GA (Fo-GA) should not be considered interchangeable with GA. On the other side of the debate, Dr. Klaus Schmierer from the Queen Mary University of London, UK, agreed that although biosimilars may seem more cost-effective on the surface, the negotiating power of national healthcare systems and payers could drive down the price of the brand-name biologics significantly, thus eliminating this theoretical edge.

While the majority of the audience initially voted in favor of the switch from brand name to generic drugs in MS, at the end of the debate most attendees shared the more skeptical view expressed by Dr. Schmierer. We can expect this debate to be carried over into next year's program.

On the topic of MS diagnosis and monitoring, the use of cerebrospinal fluid (CSF) examinations was also debated at CONy 2019. While they have been included in the 2017 Revised McDonald criteria for the diagnosis of MS in people with clinically isolated syndrome (CIS), the inconvenience, pain, costs, and risks associated with lumbar puncture (LP) favor a careful case-by-case examination of their potential benefit over systematic implementation. At the end of the debate hosted by Dr. Uros Rot from the Ljubljana University Medical Centre, Slovenia, the voting audience was evenly split in the view that CSF is still important in the diagnosis of MS. To put this result into perspective, a pre-debate survey showed that responders where unanimously in favor of the diagnostic relevance of CSF.

The case against CSF examinations was presented by Dr. Brian Weinshenker from the Mayo Clinic in Rochester, Minnesota. In his argument, Dr. Weinshenker emphasized the importance of not causing harm to the patients by conducting invasive tests when they have no predictive value. In the pro-CSF corner, Dr. Konrad Rojdak from the Medical University of Lublin, Poland, reminded the audience that MS is a complex disease requiring a complex diagnostic approach. In his expert opinion, CSF examinations remain an important component in the diagnosis of MS to avoid potentially serious consequences of misdiagnosis.

References

1. CONy 2015 Program. Available at: http://www.comtecmed.com/cony/2015/program.aspx. Accessed on 8 April 2019.

JOB CODE:
HQ/CNS/19/0010

DATE OF PREPARATION
APRIL 2019