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PEER-REVIEWED CONFERENCE REPORT

Atogepant prevents treatment-resistant migraine

Atogepant was effective in preventing difficult-to-treat episodic migraine in patients who had previously failed between 2 and 4 classes of oral preventive migraine medications in the ELEVATE trial.

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Teriflunomide prevents conversion to multiple sclerosis

Treatment with teriflunomide resulted in a 62% risk reduction for a first clinical event to the CNS compared with a placebo in patients with the radiologically isolated syndrome.

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Ravulizumab effective in AQP4+ NMOSD

In the open-label, phase 3 trial CHAMPION-NMOSD, ravulizumab significantly lowered the risk of relapse in patients with anti-aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder (AQP4+ NMOSD).

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Letter from the Editor

Dear colleagues,

This year the AAN Annual Meeting took place in Boston, being no less than the 75th edition of the yearly conference.

Healthcare professionals from around the world came together to share their insights into the latest most cutting-edge science, covering a broad range of specialities, and providing the opportunity to connect with peers and friends.

This review aims to provide summaries of the essentials of varied topics covered in the scientific sessions.

A benefit of early intervention with disease-modifying treatments was shown with the use of teriflunomide in patients with radiologically isolated syndrome. In adults with NMOSD, ravulizumab showed to lower the risk of relapse and had a good safety profile. And also in migraine research new developments were made, with atogepant effectively preventing treatment-resistant episodic migraine.

The multiple monoclonal antibody approaches to treat Alzheimer' Disease were again the focus of many contributions and intense debate.

Please enjoy the reading.

Best wishes,

Hans-Peter Hartung

Biography

Prof. Hartung is currently Professor of Neurology at Heinrich-Heine-University Düsseldorf, Honorary Professor at Brain and Mind Center, University of Sydney, Visiting Professor at Medical University Vienna and Palacky University Olomouc. He was chairman of the Department of Neurology, Heinrich-Heine-University Düsseldorf from 2001-2020, director of the Center for Neurology and Neuropsychiatry from 2012-2020 and director of the Department of Conservative Medicine from 2012-2019.

Prof. Hartung's clinical and translational research interests are in the field of basic and clinical neuroimmunology and in particular multiple sclerosis and immune neuropathies, development of new immunological, neuroprotective and neural repair promoting strategies. He has (co-)authored more than 950 articles in peer-reviewed journals and 100 book chapters. He has been involved as member of the Steering Committee in numerous international multicentre therapeutic phase 2 and 3 trials in multiple sclerosis, Guillain-Barré Syndrome and CIDP.

He was President of ECTRIMS and has served/ serves amongst others on the executive boards of the European Charcot Foundation, the European Neurological Society, and the International Multiple Sclerosis Cognition Society (IMSCOGS). He is/was also member of the Editorial Board of a number of international journals. Prof. Hartung is a Fellow of the AAN and EAN, and has been chair/ member of the management group of the EAN scientific panels on general neurology and multiple sclerosis. He is Corresponding and Honorary Fellow of several international societies.

Conflict of Interest Statement:
Hans-Peter Hartung has received fees for consulting, speaking, and serving on steering committees from Bayer Healthcare, Biogen, GeNeuro, MedImmune, Merck, Novartis, Opexa, Receptos Celgene, Roche, Sanofi Genzyme, CSL Behring, Octapharma, Teva, TG Therapeutics, and Viela Bio, with approval by the Rector of Heinrich-Heine University.

Infectious Diseases

Original antigenic sin influences humoral immune response to SARS-CoV-2

The 'original antigenic sin' may play an important role in shaping the humoral immune response to SARS-CoV-2 immunity and could consequently be a key factor in the pathogenesis of neurologic post-acute sequelae of SARS-CoV-2 (neuroPASC).

The pathogenesis of neuroPASC remains unclear. The current study concentrated on the role of the patient's antibodies and innate immune response in the mechanisms of neuroPASC [1]. Using the serum of SARS-CoV-2-infected patients who did or did not develop neuroPASC, a systems serology approach enabled unbiased in-depth profiling of antibody responses against SARS-CoV-2 and other viruses (including non-Coronaviruses). Among those patients who did not develop neuroPASC, the researchers compared serum and antibody responses to identify factors predictive of good versus bad neurological outcomes.

Of 112 patients with a SARS-CoV-2-infection, 18 developed neuroPASC. In patients with neuroPASC, all antibody isotypes/subclasses were detected in the serum, whereas the CSF was mainly populated with SARS-CoV-2-specific antibodies (IgG), and IgM antibodies were absent. This suggests a sieve and selective transfer of antibodies across the blood-brain barrier and compartmentalised humoral responses within the CSF rather than intrathecal synthesis.

Overall, patients with neuroPASC showed a lower systemic antibody response against SARS-CoV-2 than non-neuroPASC controls. In contrast, antibody responses to Epstein-Barr virus, influenza virus, or herpes simplex virus type 1 were not different between groups. Surprisingly, there were expanded antibody responses to other common Coronaviruses in the neuroPASC group, suggesting a phenomenon referred to as the 'original antigenic sin' or immunological imprinting. This phenomenon occurs when prior exposure to an antigen shapes the subsequent (suboptimal) immune response to a related antigen.

This skewed humoral response was selectively enriched in the patients with neuroPASC and poor outcomes, suggesting that the original antigenic sin effect may serve as a prognostic biomarker for neuroPASC. Mechanistically, this skewed antibody activation may reduce viral clearance and increase neuro-inflammation, contributing to neurological symptoms.

1. Spatola M. Serum and cerebrospinal fluid antibody signatures track with outcome of neurologic post-acute sequelae of SARS-Cov-2 infection (NeuroPASC). S21.006, AAN 2023 Annual Meeting, 22–27 April, Boston, USA.

Allogenic T-cell-based immunotherapy for PML in development

Australian researchers developed a novel allogeneic T-cell-based immunotherapy, CE-VST01-JC, by expanding JC polyomavirus (JCPyV)-specific T-cells from healthy donors. The clinical safety and efficacy of CE-VST01-JC for patients with progressive multifocal leukoencephalopathy (PML) will be evaluated in the global ASCEND-JC study. If successful, this T-cell-based immunotherapy could become the first PML treatment.

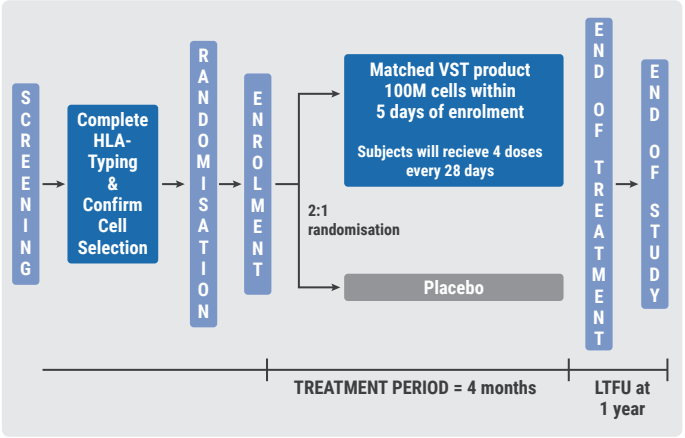
PML is a rare, devastating, and often fatal demyelinating disease of the central nervous system caused by the JCPyV. Risk groups are severely immunosuppressed patients, such as transplant recipients, HIV/aids patients, and patients with multiple sclerosis using specific medications, and the increasing use of immunosuppressive treatments in the past years has caused a rise in the prevalence of PML cases. There is currently no treatment for PML.

First author Dr George Ambalathingal (QIMR Berghofer Medical Research Institute, Australia) emphasised T-cell therapy has been highlighted as a promising approach for PML treatment over the past decade, especially JCPyV-specific or BK polyomavirus (BKPyV)-specific T-cell products [1]. In collaboration with Cellevolve, Dr Ambalathingal's group developed a novel allogeneic, off-the-shelf immunotherapy, CE-VST01-JC, consisting of JCPyV-specific T-cells from healthy donors. These T-cells were expanded using a targeted, highly curated peptide mix, consisting of 36 JCPyV-specific peptides derived from all 5 antigens of JCPyV (i.e., LT, ST, VP1, VP2, and VP3), covering 32 class I and class II human leukocyte antigen (HLA) alleles. The peptide mix was extensively assessed for JCPyV-specificity, allogenicity, and functionally and phenotypically characterised. The results

showed high specificity and more immunogenic precision with a minimised risk of graft-versus-host disease (GvHD). The in vitro characterisation indicated that CE-VST01-JC contains highly potent JCPyV-specific T-cells with stem-cell-like memory T-cells, lacking any off-target reactivity.

The clinical safety and efficacy of CE-VST01-JC will be evaluated in the multicentre, randomised, double-blind, phase 2 study ASCEND-JC (NCT05541549), with an adaptive design (see Figure). The FDA recently approved the trial, which should start in late 2023 or early 2024. Up to 60 participants will be randomised 2:1 to 4 infusions of 100 million cells of HLA-matched JCPyV-specific T-cells each, or placebo. Dr Ambalathingal explained it would be the largest trial of a PML treatment ever. Meanwhile, both CE-VST01-JC and T-cell treatments for the BK-virus (CE-VST01-BK) have become available in Australia for compassionate use. He noted that the results in 12 participants were very promising and encouraging.

Figure: Design of ASCEND-JC, a global pivotal phase 2 trial [1]



HLA, human leukocyte antigen; VST, CE-VST01-JC; LFTU, lost to follow up rate.

1. Ambalathingal GR, et al. CE-VST01-JC: A novel allogeneic T-cell based immunotherapy for the treatment of progressive multifocal leukoencephalopathy (PML). PL4.001, AAN 2023 Annual Meeting, 22–27 April, Boston, USA.

Cognitive Impairment and Dementia

Lecanemab may slow decline of cognition and function in Alzheimer's Disease

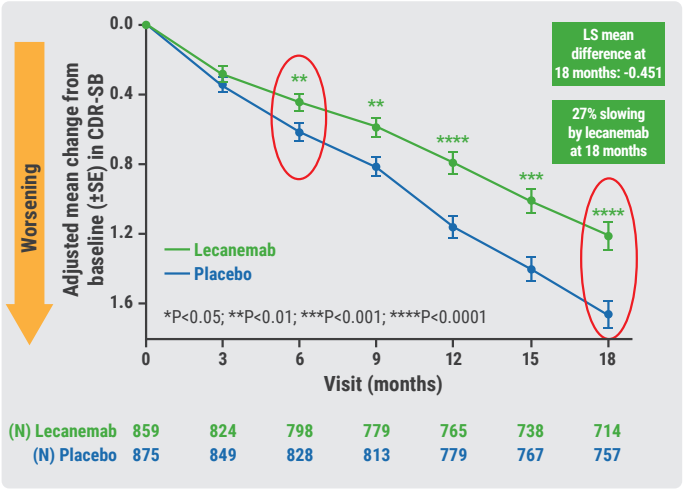
In the placebo-controlled CLARITY AD study, lecanemab slowed the decline in measures of cognition and function in early Alzheimer's Disease (AD) at 18 months. Lecanemab reduced markers of amyloid and tau indicating disease modification.

The study results were presented by Prof. Christopher van Dyck (Yale School of Medicine, CT, USA) [1]. He said accumulating soluble and insoluble aggregated amyloid-beta (Aβ) may initiate or potentiate AD pathology. Lecanemab is a humanised immunoglobulin G1 (IgG1) monoclonal antibody that highly selectively binds to Aβ aggregate species and initiates microglial-mediated clearance of protofibrils and plaques.

The global, double-blind, parallel-group, phase 3 CLARITY AD trial (NCT03887455) aimed to confirm the safety and efficacy of lecanemab compared with a placebo in participants with early AD [2]. At randomisation, the 1,795 participants were 50–90 years of age with mild cognitive impairment or mild dementia due to AD, with confirmed amyloid pathology. In the 18-month randomisation phase, they were assigned 1:1 to receive intravenous lecanemab 10 mg/kg biweekly (n=898) or a matching placebo (n=897). In the open-label extension phase, all participants received lecanemab. The primary endpoint was the change in the score on the Clinical Dementia Rating–Sum of Boxes (CDR-SB; range 0 to 18) after 18 months.

The mean CDR-SB score at baseline was approximately 3.2 in both groups. Lecanemab significantly slowed disease progression on CDR-SB by 27% at 18 months and at all time points, beginning at 6 months (see Figure). The adjusted least-squares mean change from baseline was 1.21 in the lecanemab group versus 1.66 in the placebo group (difference -0.45; 95% CI -0.67 to -0.23; P<0.001). A slope analysis using CDR-SB showed a 32% annual slowing of the slope (18–46%; P=0.00001) compared with the placebo. This means that the lecanemab group took 25.5 months to reach the same level of CDR-SB scores as the placebo at 18 months.

Figure: Lecanemab significantly slowed disease progression on CDR-SB at all time points, beginning at 6 months. Adapted from [1,2]



CDR-SB, Clinical Dementia Rating–Sum of Boxes; LS, least squares; SE, standard error.

In an exploratory analysis, lecanemab also showed consistent benefits in health-related quality of life measures and caregiver burden across different scales, Prof. Van Dyck added. The safety profile of lecanemab was acceptable: lecanemab resulted in infusion-related reactions in 26.4% and amyloid-related imaging abnormalities with oedema or effusions (ARIA-E) in 12.6% of participants.

Biomarker studies using PET and cerebrospinal fluid and plasma analyses revealed that lecanemab improved both essential biological features of AD: amyloid and tau. "This indicates disease modification, which is unprecedented in AD", highlighted Prof. van Dyck. The recruiting AHEAD 3-45 Study (NCT04468659) will evaluate whether earlier (presymptomatic) and longer intervention may be associated with an even greater effect size. Presymptomatic patients are defined by age (55–80 years old), Clinical Dementia Rating of 0, Mini Mental State Examination score ≥27, Wechsler Memory Scale-Revised Logical Memory subscale II score of ≥6, and elevated brain amyloid pathology. For patients ≤64 years of age, 1 of the following additional risk factors is required: first-degree relative diagnosed with dementia onset before age 75, known to possess at least 1 apolipoprotein E4 variant allele, or known before screening to have elevated brain amyloid according to previous PET of CSF testing.

1. Van Dyck CH. A study to confirm safety and efficacy of lecanemab in participants with early Alzheimer's disease (CLARITY AD). PL5.005, AAN 2023 Annual Meeting, 22–27 April, Boston, USA.
2. Van Dyck CH, et al. N Engl J Med 2023; 388:9–21.

Donanemab shows rapid and deep plaque clearance in early Alzheimer's Disease

More patients with early symptomatic Alzheimer's Disease (AD) reached amyloid clearance and plaque reductions at 6 months with donanemab than with aducanumab in the TRAILBLAZER-ALZ 4 study. Donanemab's rapid and deep plaque clearance was associated with improvements in plasma phospho-tau, a key biomarker of AD.

TRAILBLAZER-ALZ 4 (NCT05108922) is the first study to directly compare disease-modifying therapies in patients with early AD, said Prof. Stephen Salloway (Warren Alpert Medical School of Brown University, RI, USA) [1]. The phase 3 trial was a randomised, open-label, parallel-group study performed in 31 centres across the USA. Participants were 50–85 years old with early symptomatic AD. They were stratified on APOEε4 status and amyloid burden at baseline. Participants randomised to donanemab could discontinue treatment on meeting predefined brain amyloid clearance criteria.

After 7 weeks of screening, 148 participants were included and 74 were assigned to each group. For aducanumab, US-approved label dosing was used; for donanemab, the following clinical trial protocol was applied: 3 doses of IV 700 mg donanemab every 4 weeks, followed by 1400 mg every 4 weeks. The co-primary endpoint was amyloid clearance (to <24.1 cl) at 6 months in the full-analysis set and in the intermediate tau-subpopulation.

Upon assessing florbetapir (18F) PET scans at 6 months, the researchers found that 37.9% of participants in the donanemab group met the co-primary endpoint in the full-analysis set, compared with 1.6% in the aducanumab group (P<0.001). In the intermediate tau subpopulation, these percentages were 38.5 and 3.8, respectively (P=0.008). Donanemab was also superior in reducing plasma phosphor-tau (P-tau217).

The safety profiles of both treatments were consistent with previous study data. "Despite the greater clearance of amyloid in the donanemab group, there was no difference in the incidence of amyloid-related imaging abnormalities (ARIA) characterised by either oedema and effusion (ARIA-E) or cerebral micro-haemorrhages (ARIA-H)," finished Prof. Salloway. The TRAILBLAZER-ALZ 4 study is ongoing; analyses at 12 and 18 months are underway.

1. Salloway SP, et al. Direct comparison of donanemab to aducanumab on amyloid lowering in early, symptomatic AD: TRAILBLAZER-ALZ 4 topline study results. S26.009, AAN 2023 Annual Meeting, 22–27 April, Boston, USA.

Epilepsy

Seizure forecasting and detection with wearable devices are feasible

Wearable watches and a subcutaneous EEG device can independently and accurately forecast seizures in epilepsy patients. This is an important finding, as epilepsy patients consistently rate the unpredictability of seizures as one of the most limiting aspects of epilepsy.

Dr Benjamin Brinkmann (Mayo Clinic, MI, USA) and his consortium investigated various technological approaches to forecast seizures, including wearables, smartphone apps, and minimally-invasive devices [1]. Here, he allowed himself a joke: "Initially, we considered leveraging the popularity of seizure alert dogs in a wearable system, but we quickly discarded this idea out of concerns for chronic shoulder pain, as well as a possible high false-alarm rate due to cats, mail carriers, and tennis balls." Dr Brinkmann's consortium opted instead to evaluate 2 wearable biosensors, the wrist-worn Empatica E4 and Fitbit Inspire. When discharged from the hospital, study participants received both devices, to use one while charging the other. Participants were given 1 of 3 ambulatory EEG monitoring devices for seizure confirmation: UNEEG, SubQ, or EpiMinder. Wearable and EEG data from enrolled participants were recorded for 8 months or more. Self-reported electronic seizure diaries and periodic mood and symptom surveys were recorded by participants as well.

Of the 39 included participants, only 5 discontinued during follow-up. Over 17,000 days (approx. 46 years) were recorded with over 1,700 seizures. Using the Empatica E4 device for at least 6 months, seizure forecasting was better than chance in 5 of 6 so far studied participants, with a mean AUC (area under the receiver operating characteristics curve) of 0.80. Dr Brinkmann: "On average, we predicted 2/3 of their seizures, with about 30 minutes of pre-seizure warning, and several false alarms." He added that a data science contest on the open platform https://eval.ai replicated these outcomes. "But we do think more progress is needed to improve performance." In 5 of 6 patients that could be studied, the sub-scalp EEG signals also independently helped to forecast seizures [2].

Using an additional cohort of 65 app users, Brinkmann's group looked for possible premonitory seizure symptoms in the next 24 hours. "Interestingly, we found a strong relation between impending self-reported seizures and patients' perceived risk as well as recently reported seizures." Mood, sleep quality, and recent seizures were significantly predictive of seizures. These data are expected and were not yet published at the time of the AAN meeting.

1. Brinkmann B. Seizure forecasting and detection with wearable devices and subcutaneous EEG – outcomes from the My Seizure Gauge trial. PL4.001, AAN 2023 Annual Meeting, 22–27 April, Boston, USA.
2. Viana PF, et al. Epilepsia, 2022;April 8. DOI: 10.1111/epi.17252.

Encouraging first results of GABAergic interneurons implants for focal epilepsy

A first-in-human study evaluated the use of GABAergic interneurons (NRTX-1001) for drug-resistant focal epilepsy. Preliminary results of the first 2 participants show that both participants had over 90% seizure reduction since surgery.

NRTX-1001 cells are embryonic stem cells differentiated into pallial medial ganglionic eminence-type GABAergic interneurons. They are post-mitotic and do not proliferate. In mice with kainate-induced mesiotemporal sclerosis, implantation of these cells resulted in 66% of mice being free of focal seizures. The interneuron cell therapy also reduced hippocampal damage and increased survival in these mice.

A first-in-human, phase 1/2 clinical trial (NCT05135091) investigates whether implantation of human NRTX-1001 neural cell therapy can lead to seizure control in drug-resistant mesial temporal lobe epilepsy [1]. Participants receive immunosuppression starting 1 week before surgery and tapered after 1 year. Treatment consists of a stereotactic one-time injection along the long axis of the hippocampus with intraoperative MRI imaging. The trial follows a 2-stage design: in the open-label phase 1, 10 participants receive low- or high-dose treatments. In the double-blind phase 2, 20 participants receive cell implantation and 10 participants sham treatment. The primary endpoint is the incidence of serious or severe adverse events. Key secondary endpoints include a reduction in seizures and responder rate. Participants are between 16 and 65 years of age, have focal seizures clinically defined as temporal lobe epilepsy, and have failed to achieve seizure control on at least 2 anti-seizure medications.

Prof. David Spencer (Oregon Health & Science University, OR, USA) presented the results of the first 2 enrolled participants [1]. The first participant was a 26-year-old man who had had seizures since the age of 19. Before treatment, he averaged 32 seizures per month and treatment with 4 anti-seizure medications had previously failed. At 8 months follow-up after NRTX-1001 cell therapy, the participant had a 93% seizure reduction from baseline and had not had a focal awareness-impaired seizure since the first month.

The second participant was a 59-year-old woman who had had seizures since she was 50, had previously failed on 3 anti-seizure medications, and averaged 14 seizures a month. After 2 months of follow-up after NRTX-1001 cell therapy, she had experienced just 1 seizure.

The observed adverse events after surgery were non-serious and of mild severity in both participants. None of the adverse events were deemed related to cell therapy, some to immunosuppression. Prof. Spencer said he was excited about the first results of this novel therapy.

1. First-in-human trial of NTRX-1001 GABAergic interneuron cell therapy for treatment of focal epilepsy - emerging clinical trial results. ES1.007, AAN 2023 Annual Meeting, 22–27 April, Boston, USA.

Headache and Migraine

Lecture on migraine: from the prodromal phase to future paradigm shifts

At the AAN 2023 meeting, Prof. Peter Goadsby (King's College London, UK) was honoured with the Robert Wartenberg Lectureship. In his lecture, Prof. Goadsby reflected on the road to identifying successful therapeutic targets and developing therapeutics for migraine. He stressed the importance of prodromal symptoms, often mistaken for triggers. He also predicted 2 paradigm shifts.

"Prof. Goadsby is the type of clinician-scientist who nearly single-handedly by this pursuit changed the treatment paradigm in the field of migraine by advancing insights into the pathophysiology of a complex disease that was already believed to have been understood" [1]. These introductory words came from Prof. Natalia Rost (Massachusetts General Hospital, MA, USA). In his following lecture, Prof. Goadsby described the current armamentarium of migraine medications, including triptans, monoclonal antibodies, gepants, ditans, and neuromodulation techniques, and the underlying biology. He stressed the importance of including participants in migraine clinical trials who have previously failed on other agents, not only because they lower placebo rates, but also because these are the patients you often encounter in clinical practice.

One of the central ideas Prof. Goadsby discussed was that of migraine as a network disorder with many targets. "Migraine is typically thought of as a linear process. I think that is a too-limited view of what is a complex, networked neurological disorder. Think of the phases of migraine not linearly but as integrated; think of the symptomatology as a totality." He advised the audience to go through all symptomatology with patients. "Put it in people's minds. It only takes about 5 minutes extra."

According to Prof. Goadsby, prodromal (premonitory) migraine symptoms are easily confused with triggers. For example, about 5% of patients experience photophobia in the prodromal phase, so they will often consider light a trigger. Or they experience food cravings in the prodromal phase and assume food to be a trigger when it is, in fact, a prodromal symptom. "A patient can feel empowered just by hearing this explanation."

A possible paradigm shift Prof. Goadsby predicted, centred around pituitary adenylate cyclase-activating polypeptide (PACAP). This is a secretin/glucagon superfamily peptide with a saturable transport system into the brain. Research by Prof. Goadsby and others from the past 30 years revealed that PACAP is elevated in migraine without aura and can be normalised with sumatriptan [1]. These data already suggested that PACAP (or its receptors) could be a promising target for migraine therapeutics.

Only a few days before the lecture by Prof. Goadsby, positive phase 2 proof-of-concept results of the HOPE

trial (NCT05133323) on Lu AG09222 in migraine prevention were announced [2]. Lu AG09222 is a monoclonal antibody that binds and inhibits signalling mediated by the pituitary adenylate cyclase-activating polypeptide (PACAP). The double-blind, placebo-controlled HOPE trial assessed the efficacy, safety, and tolerability of a single intravenous infusion of Lu AG09222 in 237 migraine patients. It resulted in significantly fewer monthly migraine days in weeks 1–4 compared with placebo (P=0.01). The full trial results are not yet available.

Another paradigm shift could be using gepants in the prodromal stage of migraine. This was precluded by results of the UBR Prodrome study (NCT04492020) presented at the AAN 2023 meeting [3]. This placebo-controlled cross-over study evaluated the efficacy, safety, and tolerability of ubrogepant 100 mg when administered during the prodrome of a migraine attack. Participants treated 2 events that qualified as prodromal, meaning they were confident a headache would follow these events between 1 and 6 hours later. In 477 participants, 45.5% of treated prodromal events in the ubrogepant group were followed by the absence of moderate/severe headache within 24 hours, compared with 28.6% of events in the placebo group (P<0.0001). The number of symptoms and time to absence after treatment were also shorter than with a placebo. Prof. Goadsby: "Why is this important? Because 75% of people have some form of disability during the prodromal phase of migraine. That is what we neurologists are about, namely treating people with disabling problems."

1. Goadsby P. Migraine: then, now, and tomorrow - progress through biology. PL3.004, AAN 2023 Annual Meeting, 22–27 April, Boston, USA.
2. H. Lundbeck A/S. Lundbeck announces positive phase 2 Proof of Concept results with Lu AG09222 in migraine prevention. Corporate press release, 19 April 2023.
3. Dodick DW, et al. Ubrogepant for the acute treatment of migraine when administered during the prodrome (premonitory phase): Results from a phase 3, randomized, double-blind, placebo-controlled, crossover study. S47.001, AAN 2023 Annual Meeting, 22–27 April, Boston, USA.

Atogepant helps prevent treatment-resistant episodic migraine

In the randomised, double-blind, placebo-controlled ELEVATE trial, atogepant 60 mg once daily effectively prevented difficult-to-treat episodic migraine in patients who had previously failed between 2 and 4 classes of oral preventive migraine medications. Atogepant was safe and well-tolerated.

Atogepant is an oral calcitonin gene-related peptide (CGRP) receptor antagonist (gepant) approved for treating episodic migraine and, in the USA, for the preventive treatment of migraine. The burden of migraine is higher in patients who have previously failed prophylactic treatment. The ELEVATE trial (NCT04740827) tested atogepant in treatment-refractory European and North-American participants who had 4 to 14 monthly migraine days (MMDs) [1]. Overall, 56% of participants had previously failed 2 classes of oral preventive medication classes, and 44% had failed 3 or more. Participants were randomised 1:1 to daily treatment with atogepant 60 mg or a placebo. The primary endpoint was the change from baseline in mean MMDs over 12 weeks.

The efficacy analysis population comprised 309 participants, with 154 (50%) in the atogepant group. After 12 weeks, the decrease in MMD in the atogepant group was significantly larger (mean -4.20 days) than in the placebo group (-1.85 days; P<0.0001). Patients also significantly improved on all secondary endpoints with atogepant versus placebo, including a 50% or greater reduction in MMDs, change in mean monthly headache days, and change in acute migraine drug use days over 12 weeks. The 50% responder rate was 50.6% and 18.0%, respectively.

There were no new safety signals. The most common treatment-emergent adverse event (TEAEs) was constipation, which occurred in 10.3% of the atogepant group versus 2.5% in the placebo group. The 3 other most common TEAEs were COVID-19 (8.3% vs 9.6%), nausea (7.1% vs 3.2%), and naso-pharyngitis (5.1% vs 7.6%).

A limitation of the study was its short 12-week time frame. However, longer duration poses a general (ethical) problem for migraine trials. The long-term efficacy and safety of prophylactic atogepant are yet to be determined.

1. Pozo-Rosich P, et al. Atogepant for the preventive treatment of migraine among participants with episodic migraine with prior treatment failure: Results from the ELEVATE trial. ES2.007, AAN 2023 Annual Meeting, 22–27 April, Boston, USA.

Zavegepant nasal spray exhibits good efficacy and safety in acute migraine

In a phase 3 trial, zavegepant 10 mg nasal spray was effective for the acute treatment of migraine, demonstrating onset of efficacy as early as 15 minutes post-dose, with sustained benefit. Zavegepant had a favourable safety and tolerability profile: most adverse events were mild or moderate and none were serious.

Non-oral acute therapies for migraine are recommended when oral forms are associated with inadequate response, slow onset of action, or poor tolerability. Rapid onset effect is

a priority for many patients with migraine, said Prof. Richard Lipton (Albert Einstein College of Medicine, NY, USA), who presented the study results [1]. He added that most migraine patients prefer nasal sprays to injectables. Zavegepant is the only small-molecule calcitonin gene-related peptide (CGRP) receptor antagonist delivered by nasal spray in late-stage development for the acute treatment of migraine. Its effects and safety were compared with a placebo in a phase 3, double-blind, randomised trial (NCT04571060).

The participants were adults with typically 2–8 moderate or severe monthly migraine attacks. They self-administered 1 dose of 10 mg zavegepant nasal spray or a matching placebo to treat 1 migraine attack. The coprimary efficacy endpoints were freedom from pain and freedom from the most bothersome symptom 2 hours after the intervention.

Table: Secondary efficacy endpoints in a pre-specified hierarchical order [1]

	Zavegepant Nasal Spray 10 mg	Placebo	P-value[a]
Pain relief at 2 hours post-dose	**366/623 (58.7)**	**321/646 (49.7)**	**0.0012**
Return to normal function at 2 hours post-dose[b]	**204/570 (35.8)**	**152/593 (25.6)**	**0.0001**
Sustained pain relief from 2 to 24 hours post-dose	253/623 (40.6)	213/646 (33.0)	0.0048
Sustained pain relief from 2 to 48 post-dose	**225/623 (36.1)**	**191/646 (29.6)**	**0.0130**
Sustained pain freedom from 2 to 24 hours post-dose	91/623 (14.6)	63/646 (9.8)	0.0076
Sustained pain freedom from 2 to 48 hours post-dose	77/623 (12.4)	56/646 (8.7)	0.0308
Phonophobia reedom from 2 hours post-dose[c]	167/407 (41.0)	139/425 (32.7)	0.0123
Photophobia reedom from 2 hours post-dose[c]	207/558 (37.1)	167/585 (28.5)	0.0018
Pain relief at 60 minutes post-dose	270/623 (43.3)	241/646 (37.3)	0.0293
Return to normal function at 60 minutes post-dose[b]	115/570 (20.2)	92/593 (15.5)	0.0362
Pain relief at 30 minutes post-dose	190/623 (30.5)	131/646 (20.3)	<0.0001
Return to normal function at 30 minutes post-dose[b]	**60/570 (10.5)**	**36/593 (6.1)**	**0.0059**
Pain relief at 15 minutes post-dose	**99/623 (15.9)**	**52/646 (8.0)**	**<0.0001**
Return to normal function at 15 minutes post-dose[b]	19/570 (3.3)	12/593 (2.0)	0.1826
Rescue medication use within 24 hours post-dose[d]	184/620 (29.7)	230/643 (35.8)	0.0194
Nausea freedom at 2 hours post-dose[c]	199/380 (52.4)	206/405 (50.9)	0.6753
Pain relapse from 2 to 48 hours post-dose[e]	60/147 (40.8)	34/96 (35.4)	0.3944

[a]Cochran-Mantel-Haenszel test stratified by preventive migraine medication use at randomisation; [b]Among participants with functonal disability at time of dosing; [c]Among participants with the symptom present at time of dosing; [d]Participants with rescue medication start date on or before the study drug start date + 1 day and missing rescue medication start time were excluded; [e]Among participants with pain freedom at 2 hours post-dose.

Participants had a mean age of 41 years; 83% were women. The most bothersome symptom was photophobia in 60.4%, nausea in 24.7%, and phonophobia in 15.0%. A total of 1,269 participants were evaluable for efficacy. Prof. Lipton said that zavegepant nasal spray relieved pain as early as 15 minutes post-dose (15.9% vs 8.0%; P<0.0001). Within 2 hours of administration, significantly more patients achieved freedom from pain (23.6% vs 14.9%; P<0.0001). Zavegepant was superior to the placebo in 13 prespecified secondary endpoints (see Table). Among these endpoints, Prof. Lipton highlighted a return to normal function after 2 hours ("a highly significant difference") and sustained pain relief 15 minutes post-dose, both of which are highly valued by patients.

Most adverse events were mild or moderate; none were serious. The most common adverse events were dysgeusia (20.5% vs 4.7%), nasal discomfort (3.7% vs 0.8%), and nausea (3.2% vs 1.1%). There was no signal of hepatoxicity.

Additional trials are needed to establish the long-term safety and consistency of effect across attacks. In conclusion, Prof. Lipton said: "It is exciting to now have a non-oral option for migraine patients who benefit from the class of CGRP receptor antagonists."

1. Mullin K. Efficacy and safety of zavegepant nasal spray for the acute treatment of migraine: Results of a Phase 3 double-blind, randomized, placebo controlled trial. PL5.002, AAN 2023 Annual Meeting, 22–27 April, Boston, USA.

Simultaneous head-to-head comparison of 25 migraine medications

Triptans, ergots, and anti-emetics emerged as the most effective medications from an international study simultaneously comparing 25 acute migraine medications head-to-head. From their big-data analysis approach, analysing close to 11 million patient records of migraine attacks, the researchers concluded that the results offer generalisable insights that complement clinical practice.

A head-to-head comparison of treatment effectiveness based on real-world patient experience of this scale had yet to be performed. The American-Japanese group had consented access to 10,842,795 records of migraine attacks, which had been gathered in a smartphone application featuring an e-diary called Migraine Buddy [1]. A filtering criterium was 'English speaking user.' The researchers focused on 25 acute medications in 7 classes: acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), triptans, combination analgesics, ergotamines, anti-emetics, and opioids. Due

to the relatively low number of users, the analysis did not include gepants and ditan. The researchers used a 2-level nested logistic regression model to estimate the odds ratio (OR) of effectiveness after adjusting for pain intensity, other concurrent medications, and the covariance within the same user for each medication.

The final analysis included 4,777,524 medication-outcome pairs from 3,119,517 migraine attacks among 278,006 users. Ibuprofen was used as the reference. Triptans were found to have the highest efficacy, with a mean OR of 4.8, followed by ergotamines (OR 3.02) and anti-emetics (OR 2.67), opioids (OR 2.49), NSAIDs (OR 1.94), acetaminophen/acetylsalicylic acid/caffeine (OR 1.69), others (OR 1.49), and acetaminophen (OR 0.83). Individual medications with the highest ORs were eletriptan (OR 6.1), zolmitriptan (OR 5.7), and sumatriptan (OR 5.2). All estimated ORs were statistically significant, except for that of acetylsalicylic acid. The nested logistic regression model achieved an excellent area under the curve (AUC) of 0.849.

1. Chiang CC, et al. Simultaneous Comparisons of 25 Acute Migraine Medications: A Big Data Analysis of 10 Million Patient Self-Reported Treatment Records From A Migraine Smartphone Application. S41.001, AAN 2023 Annual Meeting, 22–27 April, Boston, USA.

A vaccine as a potentially safe and effective immunotherapy against CGRP

UB-313 may become an affordable and convenient new option to prevent migraine. Designed to stimulate the production of endogenous antibodies against calcitonin gene-related peptide (CGRP), the vaccine UB-313 has now advanced to clinical development. The ongoing first-in-human study of UB-313 will assess the safety, tolerability, and immunogenicity of 4 selected UB-313 dose regimens in healthy adults.

The UB-313 vaccine is projected to be less expensive than the currently available CGRP inhibitors, making it a more accessible treatment option for migraineurs. The longer-lasting effectiveness would also make it more convenient to use.

Dr Jean-Cosme Dodart (Vaxxinity Inc, FL, USA) presented the ongoing phase 1 trial on UB-313 (NCT05477095) assessing safety, immunogenicity and target engagement: capsaicin-induced increase in dermal blood flow [1]. It is a single-site, randomised, double-blind, placebo-controlled, multidose regimen study of UB-313 performed at the University Hospital in Leuven, Belgium. The study duration is 44 weeks, consisting of intramuscular injections of UB-313 or placebo at week 0 (baseline, day 1), week 4 and week 12, and follow-up. Participants are healthy men and women aged 18 to 55 years without migraine.

Immunogenicity studies of UB-313 were already conducted in animal models (rodents and monkeys). UB-313 was found to induce robust anti-CGRP antibodies across species. Affinity-purified antibodies bound human CGRP with high affinity, resulting in a (dose-dependent) functional inhibition of CGRP. The properties of antibodies from immunised animals were comparable with CGRP antibodies currently on the market. The specificity of the anti-CGRP antibodies for human CGRP was very high and UB-313-induced antibodies had a stronger effect on human CGRP than on rat CGRP, despite a single amino acid substitution between species.

Preclinical toxicology studies indicated UB-313 to be safe and well-tolerated. Adverse events were limited to injection site reactions and UB-313 seems to safely overcome immune tolerance.

1. Dodart J-C. UB-313, an investigational CGRP vaccine for the prevention of migraine. ES1.005, AAN 2023 Annual Meeting, 22–27 April, Boston, USA.

Multiple Sclerosis

Transcriptome data predicts long-term outcomes in untreated PPMS patients

According to a recent study, analysing RNA sequences in peripheral blood can accurately predict disability progression and brain volume change in patients with untreated primary progressive multiple sclerosis (PPMS).

Predicting severe disease outcomes can help to identify those PPMS patients who could benefit most from early intervention.

Until now, predicting severe disease progression in untreated PPMS patients has proven to be a challenging task. Aiming

to develop a blood transcriptome-based prognostic model, the presenting Israelian group exploited their biobank of peripheral blood samples of patients with PPMS who were included in the placebo arm of the clinical ORATORIO trial (NCT01194570), which evaluated ocrelizumab in PPMS. RNA samples were sequenced on the Illumina NovaSeq S2. The researchers then predicted 12-weeks confirmed disability progression (12W CDP) during 120 weeks of follow-up by applying a 2-level cross-validation algorithm. This analysis also allowed them to predict the percentage of patients with brain volume change at weeks 24, 48, and 120.

The researchers analysed RNA samples from 65 patients with PPMS. The median age was 44 years, 21 were women, and the Expanded Disability Status Scale (EDSS) at baseline was 4.5. Of these 65 patients, 24 (37%) had 12W CDP. This was correctly classified in 90.8% of patients (95% CI 80.6–100.0) with a 10-gene classifier. At week 24, 63% of patients presented with brain volume change, followed by 57% at week 48, and 64% at week 120. Brain volume change was correctly classified in 74.0% (65.1%–83.0%), 84.0%, (75.1%–93.1%) and 82.9% (73.8%–95.6%) at weeks 24, 48, and 120, respectively.

1. Gurevich M, et al. Peripheral Blood Gene Expression Transcriptional Profiling Predicts Disease Progression in Primary Progressive Multiple Sclerosis. ES1.010, AAN 2023 Annual Meeting, 22–27 April, Boston, USA.

Positive 4-year efficacy and safety data of ocrelizumab in early MS

Intense therapy with ocrelizumab in patients with early-stage relapsing-remitting multiple sclerosis (RRMS) showed clinical remission with MRI disease activity in most patients. There were no new safety signals.

Early treatment of MS has been shown to provide significant long-term benefits in terms of EDSS compared with delayed treatment. Ocrelizumab is a recombinant, humanised immunoglobulin (Ig) G1 monoclonal antibody that selectively targets CD20-expressing B cells. The single-arm ENSEMBLE trial (NCT03085810) evaluated the safety and efficacy of ocrelizumab in treatment-naive participants with early (≤3 years) RRMS [1]. Eligible participants were aged 18–55 years, had active disease, an EDSS score ≤3.5 and ≥1 clinical relapse(s) or signs of MRI activity in the 12 months before enrolment. The 678 participants received ocrelizumab 600 mg initially as 2 intravenous infusions of 300 mg 2 weeks apart and subsequently as a single 3.5-hour 600 mg infusion every 24 weeks for 192 weeks. Dr Robert Bermel (Cleveland Clinic, OH, USA) presented the efficacy and safety data after 4 years of treatment. Key endpoints were no evidence of disease activity (NEDA)-3, annualised relapse rate (ARR), mean change in EDSS from baseline, and safety.

The median age of participants was 31 years, the mean duration since diagnosis was 0.24 years, and the mean EDSS (SD) at baseline was 1.71 (0.95). At week 192, two-thirds of participants had NEDA (n=394/593: 66.4%), 77.9% showed no evidence of clinical activity, and 85.0% showed no disease activity on MRI. Furthermore, 90.9% of participants had no relapses, and 81.8% had no 24-week confirmed disability progression. Also, 90.6% and 90.4% of participants showed no T1-weighted contrast-enhancing lesions or T2-weighted lesions, respectively. The adjusted ARR was low, 0.020 (95% CI 0.015–0.027), and EDSS improved in 22.8%, remained stable in 59.3%, and worsened in 18.0% of participants.

The safety was consistent with the known profile of ocrelizumab, with no new or unexpected signals. Throughout the trial, 647 patients (95.4%) had an adverse event, whereby 105 (15.5%) participants presented with serious events and grade ≥3 events were observed in 21 (3.1%) participants. The 6 fatalities (0.6%) comprised 2 cases of COVID-19, 2 cases of COVID-19 pneumonia, 1 case of pneumonia, and 1 case of immune reconstitution inflammatory syndrome. Serious infections occurred in 6.9% of participants.

1. Bermel RA, et al. Low Disease Activity Over 4 Years of Ocrelizumab Therapy in Treatment-Naive Patients With Early-Stage Relapsing-Remitting Multiple Sclerosis; the Phase IIIb ENSEMBLE Study. S46.005, AAN 2023 Annual Meeting, 22–27 April, Boston, USA.

Teriflunomide prevents conversion to MS in patients with RIS

In patients with a radiologically isolated syndrome (RIS), treatment with teriflunomide resulted in a 72% adjusted risk reduction compared with a placebo for a first clinical event related to the central nervous system (CNS) in the phase 3 TERIS study. These outcomes add evidence for the benefit of early intervention with disease-modifying treatment (DMT) in the demyelinating spectrum of multiple sclerosis (MS).

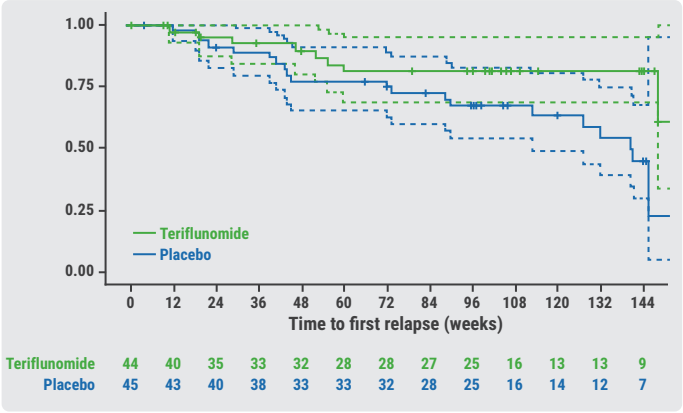
RIS represents the earliest detectable pre-clinical phase of MS. MRI features of patients with RIS are highly similar to MS, but patients do not present with clinical symptoms yet. In the previously published phase 3 ARISE trial (NCT02739542), the use of dimethyl fumarate was associated with a risk reduction for the clinical onset of MS of >80% [1]. The current

phase 3 TERIS study (NCT03122652) aimed to evaluate the efficacy and safety of the DMT teriflunomide, which has a different mechanism of action from dimethyl fumarate, in a cohort of participants with RIS from Europe and Turkey [2]. First author Prof. Christine Lebrun-Frenay (Centre Hospitalier Universitaire de Nice, France) presented the results.

The TERIS study included 89 participants aged 18 or older who fulfilled the 2009 RIS criteria. Participants were randomised 1:1 to teriflunomide (14 mg daily) or a placebo. The primary outcome measure was the time-to-onset of the first clinical symptom attributed to a CNS demyelinating event over 96 weeks. Of the randomised participants, 63 (71%) were women, the mean age was 40 years, and the age at index MRI was 38.

During 96 weeks of follow-up, 28 clinical events were detected: 8 in the teriflunomide and 20 in the placebo group. This difference was significant in both the unadjusted (HR 0.37) and adjusted analysis (HR 0.28; see Figure).

Figure: Primary endpoint analysis: risk of a first demyelinating event [2]



LCLA, low contrast letter acuity; LS mean, least squares mean; 9HPT, 9-Hole Peg test; SDMT, symbol digit modalities test; mITT, modified intention-to-treat; SEM, standard error of the mean; CI, confidence interval; mMSFC,modified MS functional composite.

Though not statistically significant, the number of new T2 and gadolinium-enhancing brain MRI lesions and PROs exploratory outcomes (i.e., cognition, quality of life, and fatigue) was also lower in the treatment group than in the placebo group. For the cumulative number of Gd+ lesions, the adjusted rate ratio (RR) was 0.33 (95% CI 0.09–1.37; P=0.086). For new or enlarging T2 lesions, the adjusted RR was 0.57 (95% CI 0.27–1.20; P=0.139). Prof. Lebrun-Frenay added that the observed safety profile was consistent with known outcomes reported in prior pivotal studies of teriflunomide.

1. Okuda DT, et al. Ann Neurol. 2023;93(3):604–614.
2. Lebrun-Frenay C, et al. Teriflunomide (Aubagio) extends the time to multiple sclerosis in radiologically isolated syndrome: The TERIS study. ES2.010, AAN 2023 Annual Meeting, 22–27 April, Boston, USA.

Gold nanocrystals may be effective as adjunctive MS therapy

The results of the VISIONARY-MS study suggest that an oral suspension of catalytically active gold nanocrystals (CNM-Au8®) given in addition to disease-modifying therapy (DMT) is effective in patients with stable relapsing multiple sclerosis (RMS). Not only vision but also global neurological function was improved.

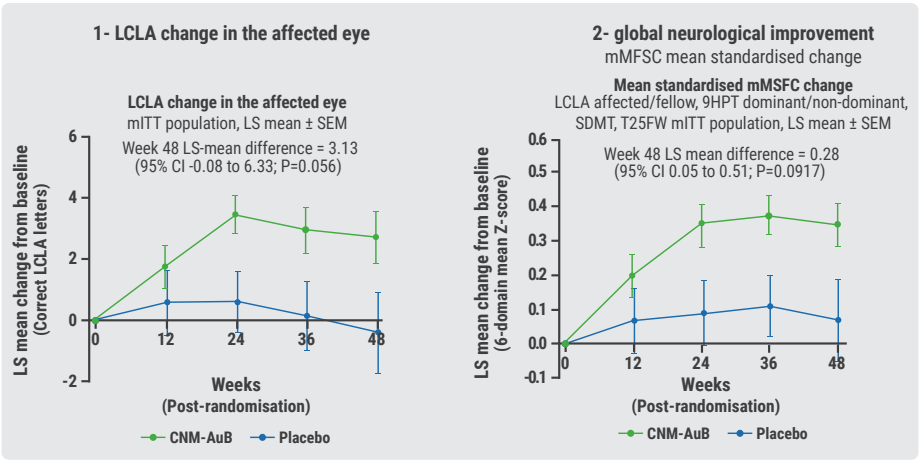
First author Prof. Michael Barnett (University of Sydney, Australia) started by recognising an unmet need: "Despite the availability of a large number of highly effective DMTs, we still do not have a therapy that promotes remyelination, and we certainly do not have a proven neuroprotective therapy for MS" [1].

CNM-Au8 is hypothesised to restore neuronal health and function by supporting brain energy metabolism. The catalytically active nanocrystals of CNM-Au8 are assumed to drive critical cellular energy, which produces reactions that enable neuroprotection and remyelination by increasing neuronal and glial resilience to disease-relevant stressors. In preclinical models, this resulted in neuroprotection and remyelination.

The current phase 2 VISIONARY-MS trial (NCT03536559) was designed as a multicentre, randomised, double-blind study evaluating CNM-Au8 versus placebo over 48 weeks in participants with stable RMS [2]. Participants were randomised 1:1:1 to CNM-Au8 15 mg/day, 30mg/day, or placebo. Prof. Barnett said the study was terminated prematurely because recruiting participants during the COVID-19 pandemic proved too challenging. Of the 150 planned participants, 73 were randomised. The participants were between 18 and 55 years of age, had RMS since <15 years, were clinically stable over the prior 6 months, and had chronic optic neuropathy, with a best corrected-low contrast letter acuity (BC-LCLA, using 2.5% low-contrast Sloan letter chart) of 20/40 or worse in the affected eye. The primary endpoint was a change in BC-LCLA score in the most affected eye up to week 48. The secondary endpoint was a global neurological improvement, measured by the modified MS functional composite (mMSFC) change up to week 48.

Both the primary and secondary clinical endpoints significantly improved (see Figure). The BC-LCLA change in the affected eye significantly differed as early as week 24. At week 48, the least squares mean difference was 3.13 (95% CI -0.08 to 6.33; P=0.056). In the CNM-Au8 group, global neurological improvement at week 48 was also more favourable than in

Figure: CNM-Au8 improves the primary and secondary clinical endpoints [1]



LCLA, low contrast letter acuity; LS mean, least squares mean; 9HPT, 9-Hole Peg test; SDMT, symbol digit modalities test; mITT, modified intention-to-treat; SEM, standard error of the mean; CI, confidence interval; mMSFC,modified MS functional composite.

the control group, with the least squares mean difference of 0.28 (95% CI 0.05–0.51; P=0.0197). The positive result of the latter endpoint was mainly driven by changes in LCLA in both eyes, in the Symbol Digit Modalities Test and the 9-Hole Peg test of the dominant hand. Prof. Barnett added that CNM-Au8 also improved independent quantitative biomarkers of enhanced axonal integrity, namely multifocal visual evoked potential amplitude and fractional anisotropy. CNM-Au8 was safe and well-tolerated; treatment-emergent adverse events were mild-to-moderate and transient.

1. Robinson AP, et al. Sci Rep. 2020;10(1):1936.
2. Barnett M. VISIONARY-MS top-line results: A Phase 2, randomized, double-blind, parallel group, placebo-controlled study to assess the safety and efficacy of CNM-Au8, a catalytically active gold nanocrystal suspension in relapsing multiple sclerosis.PL5.005, AAN 2023 Annual Meeting, 22–27 April, Boston, USA.

Stem cell therapy fails primary endpoint but improves walking in more advanced progressive MS

Treatment with intrathecal mesenchymal stem cell-derived neural progenitor (MSC-NP) therapy failed to significantly improve the Expanded Disability Status Scale (EDSS) or the EDSS Plus compared with placebo in patients with progressive multiple sclerosis (MS). However, MSC-NP may have a therapeutic effect in a subgroup of patients. A large placebo effect was observed in this study.

MSC-NPs are bone marrow-derived cells with trophic and immunomodulatory properties. Their therapeutic potential in MS was evaluated in a randomised, double-blind, placebo-controlled phase 2 trial (NCT03355365) [1]. Participants had either primary progressive disease (PPMS) or secondary progressive disease (SPMS) and a significant disability but could still walk (EDSS 3.0–6.5). The 51 participants were randomised to 6 intrathecal injections of 10 million MSC-NPs (n=24) or saline (n=27) spaced 2 months apart. The compassionate crossover design allowed participants to change to the opposite group in year 2. The primary outcome was EDSS Plus, which means improved EDSS, timed 25-foot walk (T25FW), or 9-hole peg test (9HPT).

After 1 year, no significant differences were seen in the primary endpoint. In the MSC-NP group, EDSS Plus improved in 33% of participants and in the placebo group in 37%. After 2 years, 47 participants received a placebo as well as MSC-NP. In this group, EDSS improved in 20 of 47 participants (43%), 16 participants (34%) remained stable, and 11 (23%) declined.

There were no serious adverse events related to MSC-NP treatment. A total of 7 participants withdrew from the study and no cases of meningitis or malignancies associated with the intervention were observed. Mild headaches and fever were relatively more frequent following MSC-NP treatment.

Regarding secondary endpoints, in participants with EDSS 6.0–6.5, the MSC-NP group performed significantly better than the placebo group on the T25FW (P=0.030), confirmed by the 6-minute walk test (P=0.036). In participants with less advanced grey matter atrophy, grey matter was better preserved in the treatment group (P=0.021). Furthermore, of participants with impaired bladder function, 11 of 16 (69%) in the treatment group had improved post-void residual volume versus 4 of 11 (36%) in the placebo group. A biomarker analysis revealed that MSC-NP was associated with increased matrix metalloproteinase 9 and decreased CC chemokine ligand-2 in the cerebrospinal fluid.

1. Sadiq S. Efficacy of intrathecal mesenchymal stem cell-neural progenitor therapy in progressive MS: Results from a phase II clinical trial. S16.005, AAN 2023 Annual Meeting, 22–27 April, Boston, USA.

Ravulizumab effective in AQP4+ NMOSD

In the open-label, phase 3 trial CHAMPION-NMOSD, ravulizumab significantly lowered the risk of relapse and worsening on the Hauser Ambulation Index (HAI) compared with placebo in participants with anti-aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder (AQP4+ NMOSD).

Ravulizumab binds the same complement component 5 epitope as eculizumab. However, because of its longer half-life, it can be dosed more conveniently every 8 weeks instead of every 2 weeks. The safety and efficacy of ravulizumab were evaluated in the global, open-label, phase 3 study CHAMPION-NMOSD (NCT04201262). The results were shared at the AAN 2023 meeting by lead author Dr Sean Pittock (Mayo Clinic, NY, USA) [1].

CHAMPION-NMOSD included 58 adult participants with anti-AQP4 NMOSD who had at least 1 attack or relapsed 12 months before the screening visit. Participants were allowed to stay on stable supportive immunosuppressive therapy for the trial. All participants were given 2 meningococcal vaccines at least 2 weeks before starting the ravulizumab treatment. The placebo arm of the PREVENT Study (NCT01892345) served as an external comparator. The primary endpoints were time-to-first-on-trial relapse and relapse risk reduction (RRR). The median follow-up was 73.5 weeks for all 58 ravulizumab-treated participants and 36.0 weeks for 47 participants receiving a placebo in the PREVENT Study.

In the ravulizumab group, no participants had a relapse, compared with 20 participants in the control group (RRR 98.6%; P<0.0001). Also, significantly fewer participants in the ravulizumab group had clinically important worsening on the HAI compared with placebo: 2/58 (3.4%) versus 11/47 (23.4%; P=0.023).

In the ravulizumab group, 93.1% of participants reported treatment-emergent adverse events (AEs). Serious AEs were seen in 13.8%, including 2 cases of meningococcal infection (2.4/100 patient-years), which recovered with no sequelae. Despite a longer follow-up period in the experimental group, efficacy and safety remained consistent with the primary treatment period and no relapses were observed even after a median of 91 weeks.

1. Pittock S. Efficacy and safety of ravulizumab in adults with anti-aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder: outcomes from the phase 3 CHAMPION-NMOSD trial. S5.002, AAN 2023 Annual Meeting, 22–27 April, Boston, USA.

Muscle and Neuro-Muscular Disorders

First-ever ALS platform trial reports on outcomes of 4 treatments

The HEALEY ALS Platform Trial accelerates the path to new amyotrophic lateral sclerosis (ALS) therapies by testing multiple investigational products concurrently and sequentially. Results of 4 regimens that had concluded the randomised controlled trial (RCT) period were shared: zilucoplan, verdiperstat, CNM-Au8, and pridopidine.

The HEALEY ALS Platform Trial (NCT04297683) is a perpetual, adaptive, phase 2/3, multi-regimen trial that allows for shared trial infrastructure and shared placebo data. Prof. Sabrina Paganoni (Massachusetts General Hospital, MA, USA) said the key to successfully launching this trial was working with multiple stakeholders: industry, FDA, patients, investigators, and foundations [1]. The trial is composed of 1 (phase 2/3) protocol, over 70 enrolling sites, around 1,300 participants, and a total of 7 treatments (i.e., zilucoplan, verdiperstat, CNM-Au, pridopidine, SLS-005, trehalose, ABBV-CLS-7262, and DNL343). Key inclusion criteria included sporadic or familial ALS at least 3 years after the onset of weakness and a slow vital capacity of no more than 50% of predicted.

Each regimen is compared with a shared, continuously expanding placebo dataset (3:1). Participants were not able to choose the drug they were assigned. Interim analyses performed for early futility. The RCT period was 24 weeks, followed by an open-label extension. The primary endpoint of the RCT was a change in disease severity, measured by the ALS Functional Rating Scale-Revised (ALSFRS-R). Additional endpoints included respiratory function, muscle strength, survival, and safety. Prof. Paganoni explained that the study also provides a unique opportunity to put new ALS biomarkers and outcome measures to the test: DNA (whole-genome sequencing), neurofilaments, home spirometry, and speech analysis. She added that the study's overall objective is to provide a "go or no-go decision" for the clinical development of each regimen. A total of 653 ALS patients were randomised within the first 4 regimens, of which she presented the results.

Regimen A is zilucoplan (0.3 mg/kg daily), a complement inhibitor targeting C5, which is a terminal complement activation pathway component. After the 4th interim analysis, the trial was terminated for futility. No major safety concerns were identified. Prof. Paganoni stressed that this decision saved over 250 visits plus 5 months of operational activities.

Regimen B is verdiperstat (600 mg twice daily), a myeloperoxidase inhibitor, which was well-tolerated but failed to show differences in primary or secondary endpoints versus placebo. Like regimen A, it received a "no-go decision".

Regimen C is CNM-Au8 (30 or 60 mg daily), an oral suspension of gold nanocrystals. The treatment was well-tolerated, but after 24 weeks, no significant differences were seen in ALS severity between the pooled CNM-Au8 and the placebo group. However, consistent trends in time to clinical events (i.e., clinical worsening, permanent assistant ventilation, or death) favouring CNM-Au8 30 mg were observed. A longer phase 3 trial is needed to confirm these findings and explore survival.

Regimen D is pridopidine (45 mg twice daily), a highly selective and potent sigma-1 receptor (S1R) agonist that was well tolerated. However, after 24 weeks no differences were found in primary or key secondary clinical endpoints compared with placebo. In exploratory and subgroup analyses, pridopidine improved speech function and was associated with a reduction in neurofilament-light (NfL) levels in fast-progressing participants. A phase 3 trial is needed to confirm these results.

1. Paganoni S. Results from the first four regimens of the HEALEY ALS Platform Trial. PL5.003, AAN 2023 Annual Meeting, 22–27 April, Boston, USA.

Pridopidine for Huntington's disease fails to meet the primary endpoint

Preliminary topline results of the phase 3 PROOF-HD study revealed that pridopidine did not meet its primary endpoint in patients with Huntington's disease (HD). However, prespecified analyses, excluding patients using neuroleptics and/or chorea medications, showed beneficial effects on multiple endpoints.

Prof. Andrew Feigin (NYU Grossman School of Medicine, NY, USA) first explained: "Activation of the S1R by pridopidine positively influences multiple neuroprotective pathways that we think are relevant for multiple neurodegenerative diseases, specifically for HD. These pathways include enhancement of mitochondrial function, improvement of calcium homeostasis, growth, and maintenance of synaptic function, growth of dendritic spines, the release of neurotrophic factor, and increase in autophagy" [1]. Prof. Feigin added that significant preclinical and clinical data support the efficacy of pridopidine for HD.

The current phase 3 trial PROOF-HD (NCT04556656) randomised 480 participants with manifest HD 1:1 to pridopidine 450 mg twice daily (n=240) or matching placebo (n=240). Participants had at least 36 CAG repeats and Unified Huntington's Disease Rating Scale (UHDRS)-IS levels of no more than 90%. They were allowed antipsychotic, antidepressant, chorea, or other psychotropic medications. All participants were evaluated in-person at baseline and in weeks 4, 26, 39, 52, and 65. The primary outcome was a change from baseline to week 65 in the UHDRS-Total Functional Capacity (TFC).

In total, 458 (91.8%) participants completed treatment until week 65. Prof. Feigin noted that more participants than anticipated from previous trials took neuroleptics or chorea medication, namely 60%. In the modified intention-to-treat population, pridopidine showed no benefit over placebo in a change of UHDRS-TFC. When excluding participants using neuroleptics and/or chorea medications, there was a "suggestion of improvement" in the experimental group, but the differences did not reach statistical significance. Positive trends were observed on several Q-Motor pronation supination inter-tap-interval assessments. Also, prespecified analyses excluding participants taking neuroleptics and/or chorea medications showed beneficial effects on multiple endpoints: overall progression, Q-Motor, and cognition. The safety and tolerability profile of pridopidine were similar to placebo. Additional analyses are ongoing.

1. Feigin A. Pridopine outcome on function in HD: preliminary topline results. PL5.008, AAN 2023 Annual Meeting, 22–27 April, Boston, USA.

Parkinson's Disease

Continuous levodopa/carbidopa infusion shows favourable safety and efficacy

The 3-year results of the phase 2 BeyoND trial, showed that continuous levodopa/carbidopa infusion (ND0612) had a favourable safety profile and was well-tolerated over the long term in patients with Parkinson's disease (PD) who have motor fluctuations. Participants achieved clinically relevant increases in ON-time without troublesome dyskinesia, and a decrease in OFF-time.

The 3-year results of the BeyoND study (NCT02726386) were presented by Dr Aaron Ellenbogen (Michigan Institute for Neurological Disorders, MI, USA) [1]. This open-label, phase 2 study evaluated the long-term safety of ND0612 in participants with PD who experienced ≥2 hours of daily OFF-time. The results confirmed the previously published positive outcomes after 1 year, comprising data from 214 participants, 120 of whom completed 1 year, and 114 participants entered the extension study [2]. Dr Ellenbogen highlighted that 94 participants (82.5%) completed ≥2 years and 76 (80.1%) completed ≥3 years of ND0612 treatment; some participants were already in their 7th year. Of the 20 discontinuing participants, 10 withdrew consent and 4 experienced intolerable side effects (AEs).

At baseline, participants who entered the extension phase had a mean (± SD) OFF-time of 5.6 (± 2.9) hours and a mean Unified Parkinson's Disease Rating Scale (UPDRS) motor score of 26.1 (±12.8). Further, 57 (50%) participants presented with a modified Hoehn and Yahr Scale score of 2, as opposed to 27 (23.7%) participants with a score of 2.5 and 30 (26.3%) participants with a score of 3. Dr Ellenbogen said the systemic safety profile was comparable with the expected profiles for a levodopa/carbidopa product. In year 1 of the extension period, 73.7% of the 114 participants showed drug-related AEs. In year 2, this percentage dropped to 36.9% of 111 participants and 39.4% of 94 participants in year 3. Infusion site reactions were common, mostly mild, and rarely led to discontinuation. These reactions also decreased over time (60.5% of participants in year 1, 26.1% in year 2, and 27.7% in year 3). The incidence of infusion-site infection shifted from 19.3% in year 1 to 9.9% in year 2, and 11.7% in year 3. Dyskinesia was seen in 3.5% of participants in year 1, none in year 2, and 1.1% in year 3.

Exploratory efficacy results in 45 participants at month 36 showed a mean reduction in OFF-time of -2.81 hours. The increase in Good ON-time was 2.79 hours.

1. Ellenbogen AL, et al. Safety and efficacy of continuous subcutaneous levodopa/carbidopa infusion for Parkinson's disease. Three-year data from the open-label BeyoND study. PL4.003, AAN 2023 Annual Meeting, 22–27 April, Boston, USA.
2. Poewe W, et al. Mov Disord. 2021;36(11):2687–92.

Unilateral right STN-DBS improves verbal fluency

The decline in verbal fluency in patients with Parkinson's disease (PD) may be a question of choosing the right side for subthalamic nucleus deep brain stimulation (STN-DBS). Verbal fluency declined after unilateral left STN-DBS verbal fluency while it improved after unilateral right STN-DBS, the SUNDIAL trial suggests.

Verbal fluency often declines after bilateral STN-DBS in patients with PD. "The here presented result is very important because non-motor symptoms in PD are a very important factor for the quality of life," said Dr Victor del Bene (University of Alabama, AL, USA), who presented the results [1]. He said bilateral STN-DBS is safe and has very positive patient-reported outcomes. However, a common adverse event is a cognitive change, including a decline in verbal fluency and memory. It is unknown if this holds for unilateral STN-DB. Therefore, Dr Del Bene and his group investigated verbal fluency following unilateral STN-DBS in a subcohort of the SUNDIAL trial (NCT03353688). The larger purpose of this randomised, double-blind crossover study is to measure the clinical efficacy of directional versus omnidirectional stimulation in PD and to explore whether electrophysiology biomarkers can rapidly predict effective, well-tolerated contacts for directional DBS therapy. Dr Del Bene and his group enrolled 31 SUNDIAL participants who underwent unilateral STN-DBS. The most symptomatic side was treated resulting in 17 participants treated on their left side and 14 on their right side. At baseline and at 2, 4, and 6 months after surgery, participants underwent verbal fluency and memory assessments and the Stroop test.

At baseline, none of the participants showed signs of cognitive impairment. Verbal fluency scores were significantly lower among participants after left-side STN-DBS ($t(20.66)=-2.49$; $P=0.02$). Over 6 months of follow-up, Dr

Del Bene and colleagues observed a gradual further decline in verbal fluency in the left STN-DBS group by about 25% (P=0.02). This result was consistent with published data, according to Dr Del Bene. For participants with right-side STN-DBS, verbal fluency improved by about 25% (P<0.001). This group also showed significant improvements in the Stroop test by about 18%.

The results suggest that selecting unilateral right STN-DBS to control left-sided symptoms could reduce the likelihood of verbal fluency declines in patients with PD. Dr Del Bene concluded: "At the very least, there is no evidence of a decline in verbal fluency and response inhibition in the right-side DBS group."

1. Del Bene VA. Evidence of improved verbal fluency following unilateral right hemisphere subthalamic nucleus deep brain stimulation for Parkinson's disease. S51.003, AAN 2023 Annual Meeting, 22–27 April, Boston, USA.

Stroke

Harnessing the microbiome as a possible stroke treatment

One of the 'frontiers in neuroscience' discussed in the session of the same name was the gut microbiome as a possible therapeutic target for age-related diseases, including stroke and cognitive decline. Altering the microbiome before or after stroke has enhanced recovery in mouse models and reduced neuro-inflammation.

Prof. Louise McCullough (University of Texas Health Science Center, TX, USA) defined the microbiome as the community of microorganisms – including fungi, bacteria, and viruses – that exist in a particular environment [1]. Her talk centred on the microbiome in the gut. The gut microorganisms are dynamic and change in response to diet, medication, stressors, and environmental exposure. The bacteria in the microbiome can be helpful (commensal bacteria) or harmful (pathogenic). The microbiome produces a variety of metabolites, some of which are solely generated by the microbiome (e.g., indoles, short-chain fatty acids [SCFA]). "What we're finding now is that it is not so much the biome or the bacteria that are important but their metabolites," highlighted Prof. McCullough.

As some of Prof. McCullough's work with mouse models has shown, the biome changes with age, with increasing dysbiosis: a pathological shift in its composition. This results in 'bottom-up' signalling from the gut to the brain, possibly due to circulating factors or vagal nerve function. She observed that young mice (around 12 weeks of age) recovered much quicker after an experimental stroke than older mice (16–20 months), despite having much larger strokes. This difference was due to hypothermia, significant and persistent (up to 1-month post-stroke) inflammation, and immunosuppression in aged mice, largely caused by gut-driven bacteria. The gut structure deteriorates with age; after a stroke gut permeability worsens (especially in aged mice), which correlates with neurological deficits. The biome of aged mice was radically different from young mice and contained much more deleterious bacteria. Aged mice had fewer Bacteroidetes and more firmicutes, considered more pathogenic. Intriguingly, transplanting a young microbiome (and its metabolites) to an aged recipient replenishes the biome. A study Prof. McCullough co-authored suggested that poor stroke recovery in aged mice can be reversed via 'bacteriotherapy' given 3 days post-stroke via modulation of immunologic, microbial, and metabolomic profiles in the host [2].

In explaining this beneficial effect, Prof. McCullough emphasised the role of SCFA. She explained: "A drop in SCFA probably causes a lot of inflammation. So, after a stroke, there is a possible window of opportunity for treatment with SCFA." Indeed, giving bacterial therapy increased SCFA, and this restoration of SCFA-producing bacteria was enough to improve stroke recovery to an even larger extent than a faecal transplant. Proposed mechanisms for the therapeutic effects of SCFA include beneficial effects on goblet cells, enhancement of gut barrier integrity, and enhancement of the 'immune landscape' in the brain.

Prof. McCullough also highlighted some of her (not yet published) research on indole, a biome-derived tryptophan metabolite. Looking for a potential role of indoles in neuroprotection, she found that indoles-producing bacteria

decreased dramatically with age. Post-stroke treatment of mice with indoles decreased their neurological deficit, cerebral oedema, and infarct size. She concluded that the microbiome is malleable and thus may be an important therapeutic target for age-related diseases, including Alzheimer's disease.

1. McCullough L. Harnessing the microbiome to treat stroke and age-related cognitive decline. PL6.006, AAN 2023 Annual Meeting, 22–27 April, Boston, USA.
2. Lee J, et al. Circ Res. 2020;127(4):453–65.

Patients with a large core infarct benefit from thrombectomy

The results of the phase 3 SELECT2 trial demonstrated superior functional outcomes with endovascular thrombectomy (EVT) plus medical care compared with medical care only in stroke patients with a large core infarct. However, EVT was associated with vascular complications. Cerebral haemorrhages were infrequent in both groups.

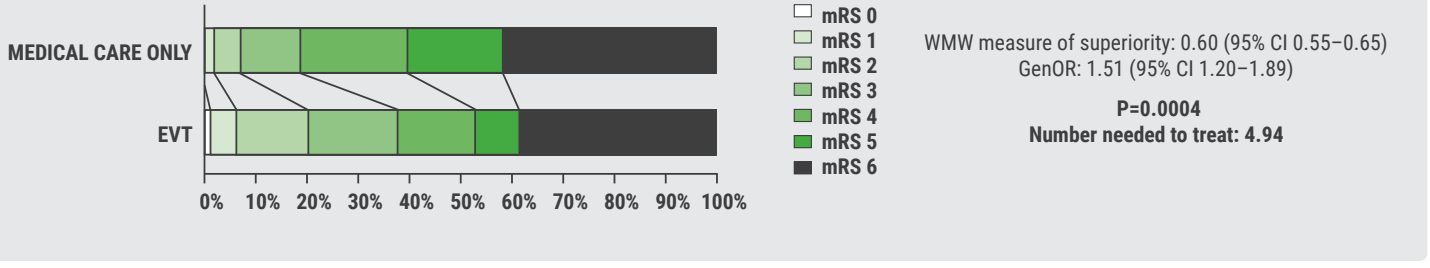
SELECT2 (NCT03876457) was a prospective, randomised, open-label, phase 3 clinical trial with blinded outcome assessment [1,2]. As 31 sites from the USA, Canada, Europe, Australia, and New Zealand participated, a covariate adaptive randomisation allowed for balanced baseline characteristics. Imaging evaluation was standardised. Participants were selected based on the presence of a stroke due to occlusion of the internal carotid artery or the first segment of the middle cerebral artery. The median ischaemic-core volume was ~80 ml (ranging from ~60 to ~120 ml). The 352 participants were randomised 1:1 to EVT plus medical care (n=178) or medical care alone (n=174). The median age was 67 years, and 73% were women. The primary outcome was the modified Rankin Scale (mRS) score at 90 days.

Leading author Dr Amrou Sarraj (UH Cleveland Medical Center, OH, USA) said that about 81% of patients in the control group had very poor outcomes at 90 days. The thrombectomy group saw a shift towards a more favourable outcome (see Figure). Dr Sarraj: "This shift translated into a 60% higher chance of improving the outcome on the mRS by at least 1 point." (Wilcoxon–Mann–Whitney measure of superiority: 0.60). At 90 days, the generalised odds for achieving a better outcome on the mRS after thrombectomy versus medical care alone was significantly higher: odds ratio 1.51 (95% CI 1.20–1.89; P<0.001). A key secondary outcome was functional independence, which was not expected to be high in this population. It was met by 20% of participants in the thrombectomy group and 7% in the medical-care group (relative risk [RR] 2.97; 95% CI 1.60–5.51); the number needed-to-treat (NNT) was 7.34. The percentage of participants with independent ambulation in the thrombectomy group was 38% versus 19% (RR 2.06; 95% CI 1.43–2.96; NNT 5.11).

Symptomatic intra-cerebral haemorrhage was infrequent and did not increase with thrombectomy (0.6%) versus medical management (1.1%; RR 0.49; 95% CI 0.04–5.36). Mortality was similar in the 2 groups: 38% versus 42% (RR 0.91; 95% CI 0.71–1.18). Early neurological worsening was increased, potentially related to infarct oedema. In the thrombectomy group, arterial access-site complications occurred in 5 participants, dissection in 10, cerebral-vessel perforation in 7, and transient vasospasm in 11 participants. Dr Sarraj concluded that these complications did not distract from the overall benefit of thrombectomy in this study population.

1. Sarraj A. A randomized trial of endovascular thrombectomy versus medical management for ischemic stroke with a large core infarct on non-contrast CT or perfusion imaging. PL5.007, AAN 2023 Annual Meeting, 22–27 April, Boston, USA.
2. Sarraj A, et al. N Engl J Med. 2023;388(14):1259–71.

Figure: Modified Rankin Scale score at 90 days [1]



WMW, Wilcoxon–Mann–Whitney; CI, confidence interval; GenOR, generalised odds ratio; EVT, endovascular thrombectomy.

Miscellaneous

Artificial intelligence applications in neurology: seize the moment

Artificial intelligence (AI) can help to stratify patients into more precise diagnostic and therapeutic categories and enable better dynamic treatment monitoring. Prof. Kathryn Davis (Penn Medicine, PA, USA) demonstrated this in a lecture by listing numerous examples, especially from her special field of interest, epilepsy [1]. "In the years to come, we will all become much more familiar with AI."

What are the current uses of AI in neurology? Prof. Davis had aptly decided to ask the ChatGPT chatbot, which listed the following examples: AI is used to diagnose diseases by analysing medical images, such as from X-ray, MRI, and CT, more accurately and quickly than humans. "Examples are breast cancer metastases and malignant pulmonary nodules on imaging," added Prof. Davis. Additionally, AI-powered virtual nursing assistants can monitor and care for patients, provide medical advice, and help with medication management. Also, regarding clinical decision-making, AI algorithms can analyse patient data and medical records, assisting doctors in creating personalised treatment plans for patients. Extending on clinical applications, robot-assisted surgery is more accurate and has a lower risk of complications, thanks to algorithms that can interpret data from surgical instruments in real time. In a more fundamental research setting, AI is used to discover new drugs, identify drug targets, and design clinical trials. Also, electronic health records are analysed with AI algorithms. And then, there is remote monitoring with AI-powered wearable devices, prompting medical intervention if necessary.

Prof. Davis focused much of her talk on the use of AI in epilepsy, where it has become so important that 2023 saw the first International Conference on Artificial Intelligence in Epilepsy and Neurological Disorders (www.aiepilepsy-neuro.com). Prof. Davis extensively exemplified the use of AI in epilepsy, noting that many of these applications are "fairly easily" translated to other neurological conditions. Here are a few examples:

1. Seizures can be forecasted, as was shown in an analysis of chronic EEG data recorded with an implanted device in drug-resistant patients; seizure probability could be forecasted up to 3 days in advance [2].
2. A machine-learning method (Clarity, Ceribell Inc.) measures the burden of seizure activity in real-time and detects status epilepticus events with high sensitivity and specificity [3].
3. Human-in-the-loop machine learning-based imaging analysis can be used to develop personalised treatment plans. This non-invasive technique detected previously hidden lesions with focal cortical dysplasia [4].
4. "AI has very good potential to change our approach to randomised controlled trials," said Prof. Davis. An example is provided by a study in which the risk of self-reported seizure within 24 hours was forecast from e-diaries [5].
5. In the My Seizure Gauge trial, seizures were forecast and detected with wearable devices and subcutaneous EEG [6].

"In the years to come I think we will all become much more familiar with AI," Prof. Davis remarked. The path forward for AI in neurology, she said, would include addressing the following issues:

- Bias in the dataset: "It is extremely important that data accurately represents the type of patient you intend to apply it to."
- Errors in data collection.
- Overreliance on AI: Not all findings of AI are reliable and translatable. "Studies must be replicable and clinically meaningful."
- The current need for regulatory guidelines on implementing AI in the clinic.
- Data privacy concerns.
- "Black box" issues: Engineers must be able to explain to clinicians how algorithms work; similarly, clinicians need to understand these algorithms to a degree and not apply them blindly in the clinic.

1. Davis KA. Artificial intelligence applications in neurology: Seizing the moment. PL2.001, AAN 2023 Annual Meeting, 22–27 April, Boston, USA.
2. Proix T, et al. Lancet Neurol. 2021;20(2):127–35.
3. Kamousi B, et al. Neurocrit Care. 2021;34(3):908–17.
4. Gill RS, et al. Neurology. 2021;97(16):e1571–e1582.
5. Goldenholz DM, et al. Ann Neurol. 2020;88(3):588–95.
6. Brinkmann B. Seizure forecasting and detection with wearable devices and subcutaneous EEG – outcomes from the My Seizure Gauge trial. PL4.001, AAN 2023 Annual Meeting, 22–27 April, Boston, USA.

Spinal cord stimulation eases painful diabetic neuropathy

10 kHz spinal cord stimulation (SCS) provided durable pain relief to patients with painful diabetic neuropathy (PDN) in the randomised-controlled SENZA-PDN trial. Treatment effects at 6 months were maintained at 24 months, and the device's safety was acceptable.

Around a quarter of all patients with diabetes experience PDN. The impact on sleep and overall quality of life is substantial. Current first-line pharmacotherapy and other types of conventional medical management (CMM) are often ineffective. Dr Erika Petersen (University of Arkansas, AR, USA) explained that SCS reduces pain by electrically stimulating neurons through leads placed in the epidural space. She presented the design and results of the SENZA-PDN study (NCT03228420) [1]. The included 216 participants from 18 USA centres had PDN for over a year, failed on at least 2 pharmacotherapies, and had lower limb pain with an intensity of ≥5 cm on a visual analogue scale (VAS) of 0–10 cm. Participants were randomised 1:1 to 10 kHz SCS plus CMM or CMM only. After 6 months, they were allowed to cross-over.

After 6 months, none of the participants chose to cross over to CMM alone, while 93% of participants in the CMM-only group did. In total (including cross-over), 181 participants received 10 kHz SCS. The trial-to-implant ratio was 85%, meaning 154 participants had permanent implants. Of these, 142 (92%) continued for 24 months of whom Dr Petersen shared the 24-month results. There were no stimulation-related neurological deficits and no explants for loss of efficacy. The infection rate was 5.2% (within the 2.5–10% range reported for SCS across patient populations), and the explant rate was 3.2% (n=5) due to infection. At 6 months, participants receiving 10 kHz SCS had an average pain decrease of 76% and an improvement in motor function and reflexes of 62%. Participants in the control group experienced an average pain increase of 2% and a functional improvement of 3%. Importantly, the pain relief was durable, as participants treated with 10 kHz SCS experienced average pain relief of 80% even at 24 months.

Neurological improvements also endured, with 66% of participants receiving 10 kHz SCS reporting maintained neurological improvements at 24 months. In line with that, a 62% reduction in sleep disturbance at 6 months was observed in the 10 kHz SCS group versus a 4% increase in the control group. At 24 months, this reduction was 66%, with a consistent treatment effect for cross-over subjects.

Discussant Dr Narayan Kissoon (Mayo Clinic, MN, USA) remarked that the sustainability of pain relief might depend on a waveform: the 1-year response for tonic stimulation was 38–56%, but 86% for high-frequency stimulation. Dr Kissoon also explained that after ~2.5 years, SCS is more cost-effective than conservative medical management and that SCS also reduces opioid use. "Any patient who has failed neuropathic pain medications and is a candidate for surgery should be considered for SCS. Almost every treated patient benefits from it, with a number needed to treat of 1.3," he concluded.

1. Petersen E. 10 kHz SCS Provides Durable Pain Relief and Neurological Improvements for Patients with Painful Diabetic Neuropathy: 24-Month RCT Results. ES1.004, AAN 2023 Annual Meeting, 22–27 April, Boston, USA.

EVT improves functional outcomes in Chinese patients with BAO

In patients with basilar-artery occlusion (BAO), endovascular thrombectomy (EVT) within 12 hours after stroke onset led to better functional outcomes at 90 days than best medical management (BMM) alone, the results of the Chinese ATTENTION trial showed. EVT was associated with procedural complications and intracerebral haemorrhage.

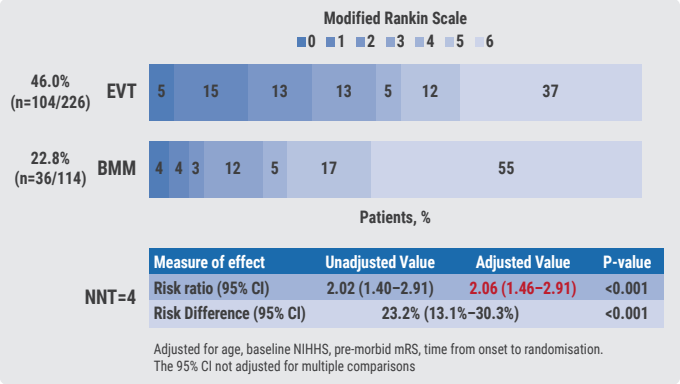
"Despite the overwhelming benefit of EVT for treating anterior circulation large vessel occlusions, it remains unknown whether EVT is beneficial for acute BAO," introduced study presenter Prof. Raul Nogueira (Grady Memorial Hospital, GA, USA). In the multicentre, prospective, randomised, controlled ATTENTION trial (NCT04751708) of EVT for BAO, 36 comprehensive centres in China participated [1]. The study evaluated the hypothesis that EVT is superior to best medical management (BMM) alone in achieving more favourable outcomes at 90 days in participants with acute BAO stroke within 12 hours from the estimated time of BAO.

The intention-to-treat population consisted of 340 participants, of whom 226 were assigned to the EVT and 114 to the BMM group. The primary outcome was good functional status as per score of 0 to 3 on the modified Rankin scale (mRS) after 90 days.

One-third of the participants received intravenous thrombolysis: 31% in the EVT group and 34% in the control group. The primary endpoint was met by 104 participants (46%) in the EVT group and by 26 (23%) in the control group (adjusted relative risk [aRR] 2.06), with a number needed to treat of 4 (see Figure). Symptomatic intracranial haemorrhage occurred in 12 participants (5%) in the EVT and none in the control arm.

Results for the secondary clinical and imaging endpoints largely went in the same direction as those for the primary outcome.

Figure: Modified Rankin Scale after 90 days. A score of 0 to 3 was defined as good functional status [1]



EVT, endovascular thrombectomy; BMM, best medical management; NNT, number-needed-to-treat; CI, confidence interval ; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.

In the EVT and the control group, 31 (13.7%) and 2 (1.8%) of participants, respectively, experienced an asymptomatic intracranial haemorrhage (ICH) at 24–72 hours; 12 (5.3%) and 0 had a symptomatic ICH, per EVT and control group, respectively. At 90 days, 83 (36.7%) participants in the EVT and 63 (55.3%) in the control arm presented with an asymptomatic ICH (adRR 0.66; 95% CI 0.52–0.82). Procedural complications occurred in 15% of the participants in the EVT-receiving group.

As Prof. Nogueira pointed out, Asians have relatively high rates of intracranial atherosclerotic disease, which limits the extent to which these findings can be generalised to Western patients. He added that the overall results of the ATTENTION trial are consistent with modern-era observational studies, large registries, and meta-analyses. The reduction in disability associated with EVT in BAO appears to be within the range of benefits observed in the anterior circulation.

1. Nogueira RG. Endovascular Treatment for Acute Basilar Artery Occlusion: A multicenter Randomized Controlled Trial (ATTENTION). PL5.006, AAN 2023 Annual Meeting, 22–27 April, Boston, USA.

Severe sleep apnoea associated with white matter hyperintensities

Reduced slow-wave sleep (SWS) and severe obstructive sleep apnoea (OSA) were associated with a higher burden of white matter hyperintensities (WMH) in a study in predominantly cognitively unimpaired, older adults. Sleep apnoea and sleep, in general, may be a target to prevent vascular contributions to cognitive impairment and dementia (VCID).

WMH are a known marker of vascular contributions to VCID in the elderly. OSA is highly prevalent among the elderly (15–65% in the community) and has been associated with mild cognitive impairment, dementia, stroke, and an increase in WMH. "There is still uncertainty about the sleep characteristics associated with WMH and associated cerebrovascular disease," said the study presenter, Dr Diego Carvalho (Mayo Clinic, MN, USA). His clinic has been conducting the population-based Mayo Clinic Study of Aging (MCSA) since 2004. The MCSA is a large-scale prospective population-based study examining the incidence, prevalence, and risk factors of mild cognitive impairment and dementia. Dr Carvalo and his group selected 140 participants without dementia who underwent at least 1 brain MRI and polysomnography (PSG) as part of their clinical care. The study aimed to determine whether PSG parameters are associated with neuroimaging biomarkers of cerebrovascular disease related to white matter integrity in older adults with OSA [1].

The 140 participants had WMH from fluid-attenuated inversion recovery (FLAIR)-MRI; 103 had fraction anisotropy (FA) of the genu of the corpus callosum (genu FA) from diffusion MRI. The mean age was 73 years and the median interval between MRI imaging and PSG was 1.74 (0.9–3.2) years. For every 10-point decrease in N3%, there was a 0.058 increase in the log of WMH (95% CI 0.006–0.111; P=0.030) and 0.006 decrease in the log of genu FA (95% CI -0.012 to -0.0002; P=0.042). "The effect size is about the same as that of 2.5 to 3 years of ageing," commented Dr Carvalo. In a posthoc analysis, participants with severe OSA had a higher WMH burden than those with mild sleep apnoea after matching for age, sex, and N3%, with a median WMH of 0.0073 versus 0.0067 (P=0.039), respectively.

Dr Carvalo stressed that no causation could be inferred from the presented cross-sectional data, but he did speculate on mechanisms of action. He suggested that lowering slow-wave sleep caused by OSA may induce axonal injury, dysmyelination, and perhaps accumulation of metabolic waste, thus contributing to WMH. He concluded that this study supports for the link between sleep depth/fragmentation, intermittent hypoxia, and vascular contributions to cognitive impairment and dementia.

1. Carvalho D, et al. Reduced Slow-Wave Sleep and Severe Sleep Apnea are Associated with Neuroimaging Biomarkers of Cerebrovascular Disease. S6.004, AAN 2023 Annual Meeting, 22–27