70th AAN Congress

American Academy of Neurology

21-27 APRIL 2018 • LOS ANGELES • USA

PEER-REVIEWED CONFERENCE REPORT

Migraine: CGRP(r)-Antagonists
Ubrogepant was shown to have clinically meaningful effects on migraine headache pain and most bothersome symptoms. Ubrogepant is the first CGRP receptor antagonist to show efficacy in treating acute migraine.

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Multiple Sclerosis: treat early
New AAN guidelines on the use of disease-modifying therapies in MS were presented at the AAN congress. They urge clinicians to discuss the benefits and risks of DMTs at an early stage of the disease.

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Thrombectomy: Wider Time Window
The DAWN trial showed the decision to perform thrombectomy in patients with acute ischemic stroke should be based on the presence of salvageable penumbral tissue rather than on a prespecified time window.

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Editor Prof. Nikolaos Grigoriadis, Aristotle University of Thessaloniki, Greece

Letter from the Editor

Prof. Nikolaos Grigoriadis

Dear Reader,

Another successful AAN meeting took place this year in Los Angeles, 21-27 April 2018. A number of studies had been announced in a broad spectrum of neurological disorders. Many studies provided updates with regard to risk-factor identification, innovative approaches in treatment, real-world data, and new clinical trials with known or new innovative compounds. Early intervention with BACE1 inhibitors, retinal changes in preclinical Alzheimer's disease and immunotherapy against amyloid-β were among the dementia-related updates. In epilepsy, transdermal cannabinoid gel usage, some updates in paediatric epilepsy and the effect of different diets in the disease are worth mentioning. The increasing interest in the use of monoclonal antibodies in the treatment of migraine was evident among the various studies presented. Some progress in movement disorders were presented, namely in new therapeutic interventions either for Parkinson's or Huntington's disease. Importantly enough, some innovative therapeutic approaches in disorders previously considered incurable and therefore lethal, such as Duchenne muscular dystrophy, SMA and ALS, indicate the potential of further development in the future. A brilliant example of the progress in this category of diseases are the FIREFISH, ENDEAR and SHINE studies in SMA. Moreover, studies indicating the extended-time window in stroke were of great importance. Last but not least, in the field of Multiple Sclerosis, the new AAN guidelines on the use of disease-modifying therapies (DMTs) were presented. In addition, interim analysis of ongoing clinical trials in SPMS or PPMS, the extended-interval dosing of Natalizumab and stem-cell transplantation in rapidly evolving severe multiple sclerosis were among the thoroughly discussed topics in the meeting.

Best Regards,
Nikolaos Grigoriadis

Biography

Dr Nikolaos Grigoriadis graduated from the Faculty of Medicine of the Aristotle University of Thessaloniki. He did his PhD thesis and residency in Neurology at the same institution. He is specialised in clinical and experimental Neuroimmunology and CNS immunopathology in a number of research centres and institutions abroad.

He is now professor and Head of the 2nd Department of Neurology, AHEPA University Hospital, the MS Centre, and the Laboratory of Experimental Neurology and Neuroimmunology.

Prof. Grigoriadis is member of various international scientific committees, such as the European School of Neuroimmunology, ParadigMS, the subcommittee of ENS for Multiple Sclerosis, the ECTRIMS committee (until 2010), the Hellenic Academy of Neuroimmunology, and president of the Hellenic Neurological Society. He is ad-hoc reviewer of international scientific journals, co-ordinator in more than 40 multicentre clinical trials for MS and principal investigator in collaborative research projects for cell therapies in CNS autoimmune demyelination.

We need more neurologists and better teamwork

Interview with AAN president
Prof. Ralph L. Sacco MD, MS, FAHA, FAAN
conducted on 25 April 2018 in Los Angeles by Michiel Tent

The AAN meeting is the largest neurological conference in the world, with over 14,000 attendants in Los Angeles in 2018, while the academy celebrates its 70th birthday. Exclusively for Medicom's *Conference Report*, AAN-president Prof. Ralph L. Sacco reflects on the meeting and on the challenges facing the academy and neurologists around the world.

With an overwhelming amount of research and new insights represented here, which topics would you consider to be of exceptional interest?

"It has been a phenomenal meeting with so much great new science across a broad spectrum of conditions: from new trials of medication to prevent and treat migraine, and breakthroughs in genetics and its implications for precision medicine, to important work sleep disorders and Parkinson's disease, to name but a few. There was something for everybody.

At the Presidential Session, Dr Francis Collins, director of the National Institutes of Health (NIH), emphasized the importance of precision medicine, in particular a new initiative called the 'All of Us Research Program'. Its ambitious aim is to enroll 1 million people in a cohort study, looking at genetics, biomarkers, and the evolution of neurological and other diseases. Dr Walter Koroshetz, director of the National Institute of Neurological Disorders and Stroke (NINDS), talked about the BRAIN Initiative. The BRAIN Initiative employs breakthrough technologies to better image connectivity in brain circuits, and to modify the nervous system in order to treat neurodegenerative diseases. The AAN feels strongly about this initiative and helps funding it. We also heard about the opioid crisis in the US and elsewhere: many people getting addicted to the opioids they receive as prescription medication, turning opioids into one of the largest growing causes of death in the US. The NIH now focuses on developing non-opioid pain treatments."

Being a stroke specialist, what are the most important developments in that area?

"Stroke is a very exciting field right now. The biggest breakthrough is expanding the time window for thrombectomy. As results of the DAWN and DEFUSE-3 trials have shown, we can treat some – well-defined – patients with large-vessel occlusion up to 24 hours post acute stroke."

What is new in the way this AAN meeting is organized?

"We continue to implement innovative changes. We still have courses and scientific sessions, but there is so much more 'bubbling' in the corridors. We call this 'experiential learning' – there are head talks, practical workshops, 'navigating your career'-sessions for every stage in your career, you can hear about and share best practices. Then there are sessions focused on wellness of the participants: yoga, music, painting... and an incredible opening party at Universal Studio's. Who says neurologists don't know how to have a good time?"

What do you think are the biggest challenges facing the field of neurology?

"Globally, neurologists are undersupplied. In the US, for example, there is often a long delay to see a neurologist. One of the biggest challenges is training more healthcare professionals to help meet the rising demands for high-quality care. The AAN has a number of exciting programs to expand the pipeline of students choosing careers in neurology to increase the supply of future neurologists. Moreover, that's where team-based care comes into play. We want the neurologist to be the leader of that team, but there are other important members to support the team including: the advanced practice provider, the physical therapist, and other subspecialists. We also aim to expand the scope of neurology practice to interventional, preventive and regenerative neurology. Traditionally, the focus has been on diagnosis, but now we have many ways to intervene. The next step is preventative neurology, which is expanding: precision medicine and biomarkers allow us to intervene in a much earlier stage. With that, we move to regenerative neurology, helping people improve their quality of life. These are therefore exciting times, with many neuroscientific breakthroughs reaching the clinic. But we need more neuroscientists and neurologists to advance this. It's a big challenge, but I think we're up to it."

Talking about challenges: how challenging has it been for you personally, to combine the AAN presidency with your work as a neurologist and professor of neurology in Miami?

"It's not easy, but I'm part of a great team. My whole life has always been about teamwork with people I can rely on including my research and my department. Likewise, in the AAN it's not about one person: I can rely on many people including the pediatric neurologist Dr Ann Tilton, the vice-president, and Dr James Stevens, the excellent president elect, and the amazing AAN staff. We're really working as a team; we 'divide and conquer'. Also, the AAN has a strategic plan: things are done in a very organized and systematic manner. All in all I can say: some days are more busy than others, but on the whole it's been fun."

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ISSN 2468-8762 18:6

Dementia

It has proven very hard to find a drug intervention that produces clinically meaningful results in established Alzheimer's disease (AD) and other dementias. This may have motivated a shift in dementia research: an increased focus on identifying patients in the preclinical stage when neuronal loss is still limited; providing a better opportunity for early intervention.

Early intervention: BACE1 inhibitors

A good example of both these observations is solanezumab, which, at a dose of 400 mg administered every 4 weeks in patients with mild AD, did not significantly affect cognitive decline [1]. The projected indication has since been limited to the treatment of preclinical stages of Alzheimer's, as Prof. L. Apostolova (Indiana University School of Medicine, USA) pointed out at a review session on dementia. Solanezumab is one of a number of beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) inhibitors currently under investigation for very early stages of AD. BACE1 inhibitors are believed to reduce the production of amyloid-β. Prof. Apostolova calls very early intervention "a great concept", which is also applied in the Longitudinal Early-onset Alzheimer's Disease Study (LEADS). This is a non-randomised, natural history, non-treatment study designed to look at disease progression in individuals with early-onset AD. Clinical/cognitive, imaging, biomarker, and genetic characteristics will be assessed across individuals with early-onset AD and cognitively normal controls [2]. "This cohort of over 18,000 participants is very important," says Prof. Apostolova, "because they are relatively young, and have few comorbidities."

Retinal changes in preclinical Alzheimer's disease

Results of one study presented at the AAN meeting, in particular, may help identify AD in a preclinical stage. Optical coherence tomography (OCT) results suggest that biomarker positive, preclinical AD subjects have retinal microvascular abnormalities in addition to foveal thinning [3]. Furthermore, patients with preclinical AD may be identifiable by OCT angiography characteristics prior to the onset of cognitive dysfunction, which could allow for early therapeutic opportunities to prevent further neuronal loss.

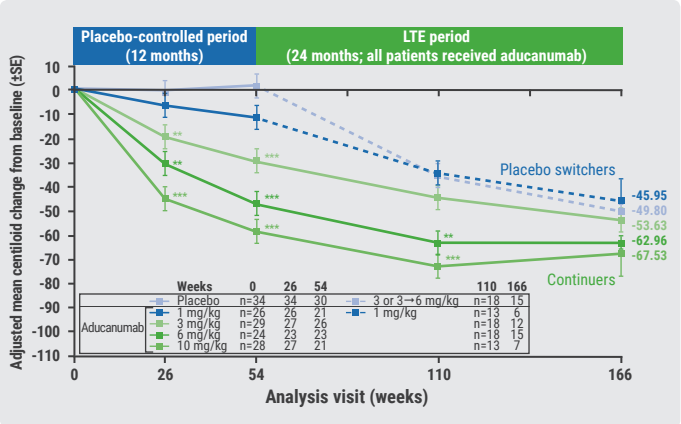
The 32 subjects enrolled in the study were cognitively normal, and separated into either biomarker positive or biomarker negative groups. Data was collected from 57 eyes from 30 patients: 16 biomarker negative, 14 biomarker positive. The foveal avascular zone was significantly increased in biomarker positive patients (0.30 mm^2 vs 0.40 mm^2, P=0.002). Inner foveal thickness was found to be thinner in biomarker positive patients: 75.4 vs 66 µm, P=0.278.

Immunotherapy against amyloid-β

The majority of disease-modifying treatments (DMTs) in development for AD are directed against the amyloid-β (Aβ) peptide. Among these, monoclonal antibodies (mAbs) are the most extensively developed. A mAb that shows positive and clinically meaningful benefits is aducanumab. The 36-month data for fixed-dose cohorts of the ongoing PRIME study were presented at the AAN meeting, including 12 months from the placebo-controlled period and 24 months from the long-term extension (LTE) [4]. During the double-blind, placebo-controlled phase, patients aged 50-90 years were randomised to fixed doses of aducanumab stratified by APOE ε4 status and received aducanumab or placebo Q4W for 52 weeks. In the LTE, all patients received aducanumab 3, 6, or 10 mg/kg fixed or titrated.

Amyloid plaque levels continued to decrease in a dose-dependent and time-dependent manner in patients from fixed-dose cohorts who completed the first 2 years of the LTE; analyses of the clinical endpoints suggest a continued clinical

Figure 1 Effect of Aducanumab on Amyloid Plaque Levels [4]



Nominal * P<0.05; nominal ** P<0.01; nominal *** P<0.001 vs placebo on the placebo-controlled period and vs placebo switchers in the LTE period

benefit (Figure 1). No new patients who continued at the same dose of aducanumab experienced amyloid-related imaging abnormalities - vasogenic edema (ARIA-E). The investigators conclude that the data supports further investigation of aducanumab in the ENGAGE and EMERGE phase 3 trials.

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Epilepsy

In a review session on paediatric epilepsy, Dr K.G. Knupp (University of Colorado Denver, USA) was enthusiastic about the many recent developments, such as a 'team science' initiative to cure infantile spasms (IS). Further, the MONEAD study showed that women who were seizure free prior to conception have a low risk for seizure recurrence during pregnancy. Another study reported transdermal cannabidiol gel reduced seizures in focal epilepsy.

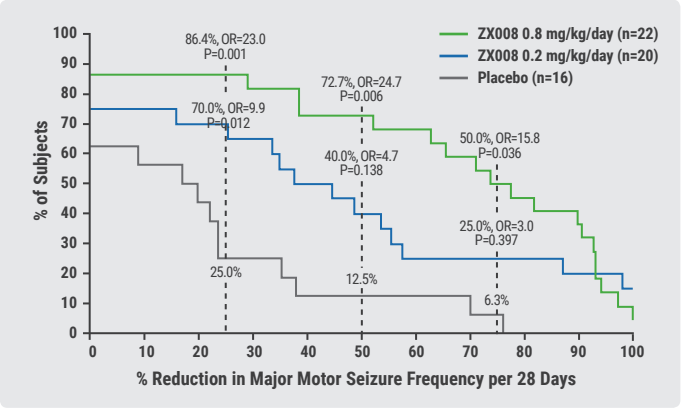
Paediatric epilepsy

In a multidisciplinary team science initiative, Citizens United for Research in Epilepsy (CURE) awarded grants to eight teams of investigators to find a cure for infantile spasms (IS) [1]. As things stand, Dr Knupp had this to say about treating IS: "If there is one thing you take away from my talk, let it be that standard medication is more effective in treating IS than non-standard medication." She also mentioned a recent study in children with refractory convulsive status epilepticus, demonstrating for the first time a link between delayed treatment (>10 minutes) and poor outcomes. Untimely first-line benzodiazepine treatment was independently associated with a higher frequency of death, use of continuous infusions, longer convulsion duration, and more frequent hypotension [2].

A form of precision medicine Dr Knupp mentioned was cerliponase alfa (BMN 190), an investigational enzyme replacement therapy designed to treat neuronal ceroid lipofuscinosis type 2 (CLN2). Schulz et al. [3] reported that intraventricular infusion of cerliponase alfa in patients with CLN2 disease showed less decline in motor and language function than in previous controls. Serious adverse events included failure of the intraventricular device and device-related infections.

Dr Knupp was also excited about the results of fenfluramine HCl oral solution (ZX008) on the frequency of convulsive seizures (FCS) in children with Dravet syndrome. At the AAN meeting, results were presented of a subgroup analysis of the effect of ZX008 in 58 subjects who discontinued stiripentol prior to entry in a phase 3 clinical study: Study 1 (n=119) [4]. In this subgroup, ZX008 provided robust improvement in FCS (Figure 1). Mean age was 9.7 years. ZX008 0.8 mg/kg/day showed a 60.8% reduction in mean monthly FCS vs placebo (P=0.002). In the 0.8 mg/kg/day group, 73% of subjects achieved ≥50% reduction in FCS (P=0.006) and 50% achieved ≥75% reduction (P=0.036). Longest median seizure-free intervals were 24.5 days in the 0.8 mg/kg/day group, compared to 9 days in the placebo group (P=0.003). ZX008 was generally well tolerated.

Figure 1 Cumulative response curve for % reduction in seizure frequency per 28 days (combined titration and maintenance periods) for patients who previously failed stiripentol [4]



OR, odds ratio

Three diets compared

Among children with drug resistant epilepsy, modified Atkins diet (MAD) and low-glycaemic index treatment (LGIT) diet were non-inferior to ketogenic diet (KD). However, in the randomised trial that established this, patients on LGIT demonstrated >50% seizure reduction, with a better safety profile [5]. Participants in this non-inferiority trial were 170 children (age 1 – 15 years) who had ≥4 seizures/month, had failed to respond to ≥2 anti-epileptic-drugs, and had not been treated previously with KD/MAD/LGIT. They were randomly assigned to receive KD, MAD or LGIT as an add-on to the ongoing antiepileptics. After 24 weeks, the mean percentage seizure reduction was -60.3 in the KD group; -47.9 in the MAD group; and -54.7 in the LGIT group. The difference was statistically insignificant (P=0.18). The mean difference in seizure reduction between KD and MAD was -12.33, and between KD and LGIT -5.66. LGIT had significantly less adverse events (AE) than KD and MAD (P=0.036). Serious AE were observed in 12/170 (7.1%) of patients, all in the KD and MAD groups.

Seizures during pregnancy

One of the studies in adult epilepsy patients that generated much attention at the AAN meeting was the observational MONEAD study [6]. This is the first study ever to compare seizure frequency changes in pregnant women with epilepsy (PWWE) to non-pregnant women with epilepsy (NPWWE). Findings suggested low risk of seizure recurrence during pregnancy for women who were seizure free prior to conception, and did not differ compared to NPWWE. MONEAD enrolled 351 PWWE and 109 NPWWE. For the 9 months preceding pregnancy, 164/351 (46.7%) women were seizure free in the PWWE group, and 49/109 (45.0%) were seizure free in the NPWWE group. Of these seizure-free women at baseline, 139 (84.8%) PWWE remained seizure free during pregnancy and 144 (87.8%) during the 9 months postpartum; 42 (85.7%) NPWWE remained seizure free for 9 months following enrolment, and 41 (83.7%) in the subsequent 9 months.

Transdermal cannabidiol gel

Transdermal cannabidiol (CBD) gel (ZYN002) reduced seizures in focal epilepsy and was well tolerated, with excellent patient compliance and acceptance, judged by results of the STAR 1 and 2 trials [7]. STAR 1 was a double-blind, placebo-controlled trial that assessed ZYN002 at 195 mg and 390 mg doses as adjunctive therapy in 188 patients. After 12 weeks, there was no significant difference in seizure frequency. STAR 2 was the open-label extension study for the 174 patients who completed STAR 1. Continued treatment with ZYN002 in STAR 2 (390 mg daily) resulted in clinically meaningful reductions observed by 6 months, which were maintained through 12 months. There was a median percent change in seizures from -16.3% at 3 months (n=170), to -27.3% at 6 months (n=148), -50.2% at 9 months (n=98), and -58.0% at 12 months (n=70). ZYN002 (administered twice daily) was well tolerated, with excellent skin tolerability.

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Headache and Migraine

A new era of migraine treatment is dawning, with the advent of the oral calcitonin gene-related peptide (CGRP) antagonists and CGRP receptor antagonists. New trial data on preventing migraine were presented on all four agents currently in development, but a small-molecule 'gepant' also generated much interest: ubrogepant. This is the first CGRP receptor antagonist to show efficacy in treating acute migraine.

mAbs, ditans and gepants

Reviewing the past year, Dr M.S. Robbins (Albert Einstein College of Medicine, USA) reminded his audience how "overwhelmingly large" the problem of headache/migraine is, being the second leading cause worldwide of Years Lived with Disability. "Even cluster headache is not rare, with a lifetime prevalence of about 1:1000."

Migraine treatment, however, is about to be revolutionised. A total of 4 oral monoclonal antibodies (mAbs) are currently in late stage development for migraine prevention. Three against CGRP itself: galcanezumab (LY2951742), eptinezumab (ALD403), and fremanezumab (TEV-48215) and one against the CGRP receptor: erenumab (AMG 334). For fremanezumab and galcanezumab, trials for cluster headache are underway. Other migraine medications under development that Dr Robbins specifically mentioned included: serotonin 5-HT1F agonists (ditans) and small molecules (gepants) targeting the CGRP receptor, such as ubrogepant. The first-in-class ditan is lasmiditan (COL-144); trials for the treatment of acute migraine (SPARTAN, GLADIATOR) are underway.

Effect of ubrogepant on headache, MBS

In the phase 3 study ACHIEVE I, ubrogepant was shown to have clinically meaningful effects on migraine headache pain and most bothersome migraine-associated symptoms (MBS). Ubrogepant was well tolerated with no identified safety concerns [1]. The randomised, double-blind, placebo-controlled ACHIEVE I study evaluated the efficacy, safety, and tolerability of ubrogepant (50 mg, 100 mg) vs placebo for the acute treatment of a single migraine attack in adults. Co-primary efficacy endpoints were pain freedom 2 hours after initial dose, and absence of the MBS.

Table 1 Co-primary endpoint results for each ubrogepant dose vs placebo (mITT population)

Endpoints	Statistics	Placebo (N=456)	Ubro 50mg (N=423)	Ubro 100mg (N=448)
Co-primary endpoint 1: Pain freedom 2 hours after initial dose	Pain free at 2 Hours, %	11.8	19.2	21.2
	Adjusted p-value	-	0.0023	0.0003
Co-primary endpoint 2: Absence of most bothersome symptom[1] 2 hours after initial dose	Absence of MBS[1], %	27.8	38.6	37.7
	Adjusted p-value	-	0.0023	0.0023

[1] Most Bothersome Symptoms including photophobia, phonophobia or nausea

Of 1672 randomised patients, 1327 were included in the mITT efficacy analysis. At 2 hours post-initial dose, significantly more treated ubrogepant-treated patients achieved pain freedom than placebo-treated patients (50 mg: 19.2%, P=0.0023; 100 mg: 21.2%, P=0.0003, placebo: 11.8%) (Table 1). The percentage of ubrogepant-treated patients achieving absence of MBS was also significantly greater (50 mg: 38.6%, P=0.0023, 100 mg: 37.7%, P=0.0023, placebo: 27.8%). The MBS was most often photophobia (56.4%). The adverse event (AE) profile of ubrogepant was similar to placebo. There was no evidence of liver toxicity.

The abstract on ubrogepant was singled out by Dr N. Rost (Massachusetts, USA), chair of the AAN science committee, as one of the highlights of the 2018 meeting. She lauded the results, but added it is too early to say where ubrogepant will fit into the treatment of acute migraine: "The bar was set low, with placebo as comparator". This was an FDA requirement. "It will be interesting to see ubrogepant compared to a triptan." In view of their different modes of action, Dr Rost said triptans and gepants probably have additive effects: a rationale for a combination therapy?

Erenumab in difficult to treat migraine

In a population of patients with difficult to treat migraine, erenumab resulted in nearly three-fold higher odds of a ≥50% reduction in monthly migraine days, with more than twice as many patients achieving this reduction taking erenumab compared to placebo. These were the main results of the LIBERTY trial [2].

LIBERTY is a phase 3b, double-blind study of erenumab in patients with episodic migraine, defined as 4 to 14 migraine

days per month at baseline. Participants had failed 2 to 4 prior preventive treatments for migraine. During the 12-week, double-blind treatment phase, 246 patients were randomised to monthly subcutaneous injections of either erenumab 140 mg or placebo. The primary endpoint was the percentage of patients with at least 50% reduction of monthly migraine days over weeks 9-12. This percentage was significantly higher with erenumab vs placebo: 30.3% and 13.7%, respectively (OR 2.73; P=0.002). Erenumab also resulted in statistically significant and clinically meaningful improvements across all secondary endpoints. The trial includes an ongoing 52-week, open-label extension study.

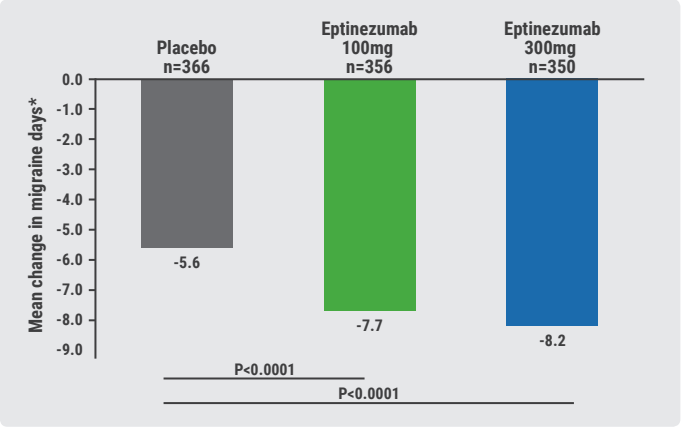
Data from another study presented at the AAN 2018 meeting indicated that erenumab has similar efficacy in patients with chronic migraine with and without aura in terms of monthly migraine days (MMD), acute migraine–specific medication days, and ≥50% responder rates (≥50% reduction in MMD) [3].

Eptinezumab: results of PROMISE 1 and 2 trials

Two pivotal phase 3 trials of intravenous eptinezumab, PROMISE 1 and PROMISE 2, both yielded positive results. In PROMISE 1, all tested doses of eptinezumab significantly reduced migraine activity through 3 months after first infusion in patients with FEM. The probability of migraine was significantly reduced on day 1 posttreatment and benefits were maintained for 3 months with a single infusion. Adverse event rates were similar to placebo [4]. Efficacy analysis included 888 patients. Mean baseline MMD were 8.5 days across groups. Eptinezumab 30, 100, and 300 mg vs placebo decreased MMD over weeks 1 12: -4.0 (P=0.0045), -3.9 (P=0.0179), -4.3 (P=0.0001) vs -3.2, respectively. More patients achieved ≥75% reduction in MMD over weeks 1 12 with eptinezumab. Approximately 50% of patients receiving eptinezumab 30, 100, and 300 mg achieved ≥50% reduction in MMD over weeks 1 12 vs 37.4% in the placebo group. These results were associated with an approximately 10-fold increase in migraine-free intervals and greater improvements in health-related quality-of-life [5].

In PROMISE 2, eptinezumab-treated patients showed significant improvements in migraine activity across the primary and all key secondary endpoints [6]. The 1072 participants had ≥15 to ≤26 headache days of which ≥8 were assessed as migraine days. They were randomised to placebo, eptinezumab 100 mg, or 300 mg. Eptinezumab significantly decreased MMD in weeks 1–12, which was the primary endpoint: -5.6, -7.7 and -8.2 days, respectively

Figure 1 Primary endpoint eptinezumab significantly decreased monthly migraine days: weeks 1–12 [6]



* Analysis of covariance model used to test for differences between treament groups

(P<0.0001) (Figure 1). In the eptinezumab 300 mg group, 33.1% of subjects achieved a ≥75% reduction in MMD; 61.4% achieved a ≥50% reduction. Eptinezumab had an instant effect: the percentage of subjects with migraine on the first day after eptinezumab infusion decreased by >50% compared with baseline, which was sustained through day 28. AE rates were similar to placebo.

Fremanezumab: evaluation of two-dose regimens

An evaluation of two subcutaneous dose regimens of fremanezumab confirmed the efficacy, safety, tolerability, and flexible dosing profile of fremanezumab for the preventive treatment of chronic migraine [7]. In this 16-week, randomised, double-blind trial, patients were assigned to 1 of 3 treatment groups:

1) monthly dosing: 675 mg fremanezumab during month 1, followed by 225 mg of fremanezumab at months 2 and 3;
2) quarterly dosing: fremanezumab 675 mg during month 1, followed by placebo injections at months 2 and 3;
3) monthly administration of matching placebo.

The primary efficacy endpoint was mean change from baseline to 12-week double-blind treatment period in monthly average number of headache days (NHD) of at least moderate severity. At the 28-day baseline period, the NHD was 13.1. Both dosing regimens of fremanezumab were associated with significant NHD reductions vs placebo: group 1) -4.6 days (P<0.0001); group 2) -4.3 days (P<0.0001), group 3) -2.5 days.

Numerous sub-analyses of trial data were presented as posters. Onset of action with fremanezumab occurred rapidly [8]. Fremanezumab treatment reduced the need for acute

headache and migraine-specific medication [9]. It also resulted in significant improvements in work productivity and activity impairment [10]. Fremanezumab demonstrated efficacy in preventive treatment of chronic migraine in patients with comorbid depression, improving symptoms of depression [11].

Galcanezumab in patients who failed ≥2 preventives

Galcanezumab (GMB) 120 mg/240 mg is statistically significantly reduced monthly migraine headache days (MHD) compared to placebo (P<0.001) in both patients who failed and did not fail ≥2 prior preventives [12]. Treatment-by-subgroup interactions may be driven by lower placebo response in patients who failed preventives previously as magnitude of change for GMB-treated patients were similar in both subgroups. This was concluded from subgroup analyses of the randomised phase 3 trials EVOLVE-1, EVOLVE-2, and REGAIN in patients with episodic (EVOLVE-1/2) or chronic (REGAIN) migraine.

For the subgroup who failed prior preventives, MHD reductions were:

- EVOLVE-1/2: placebo: 0.81; GMB 120 mg: 3.45; GMB 240 mg: 3.85;
- REGAIN: placebo: 1.44; GMB 120 mg: 5.91; GMB 240 mg: 3.30.

Significant treatment-by-subgroup interactions were seen for GMB 240mg (EVOLVE-1/2) and for GMB 120 mg (REGAIN), suggesting better efficacy compared with placebo for these doses in patients who failed prior preventives. Mean percentage of patients with ≥50% response to GMB was significantly higher for both subgroups in EVOLVE-1/2 and REGAIN.

Non-invasive vagus nerve stimulation

Results of a randomised sham-controlled trial supported the use of non-invasive vagus nerve stimulation (nVNS; gammaCore®) as a rapidly effective, well tolerated, and practical option for the acute treatment of episodic migraine [13]. Patients with episodic migraine (n=248) self-administered two 120-second stimulations bilaterally to the neck within 20 minutes of migraine pain onset for up to 5 migraine attacks. If pain did not improve at 15 minutes, patients repeated both stimulations; a third set of optional stimulations was administered by those who were not pain-free at 120 minutes. Acute nVNS treatment led to significantly higher pain-free rates than sham for the first treated migraine attack at 30 minutes: 12.7% vs 4.2% (P=0.012) and 60 minutes: 21.0% vs 10.0% (P=0.023), but not at 120 minutes: 30.4% vs 19.7% (P=0.067). A post hoc repeated measures test confirmed that nVNS was superior to sham through 120 minutes (OR: 2.3; P=0.012). Adverse effects of nVNS were infrequent and mostly mild and transient.

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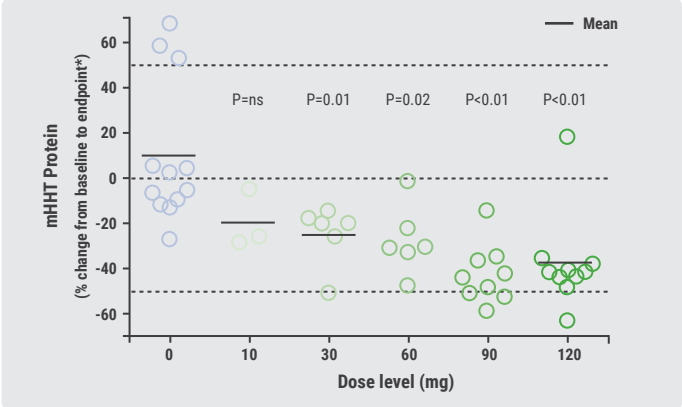
Movement Disorders

The field of movement disorders saw quite a few studies of new treatments that were tested for the very first time. One of these suggested IONIS-HTTRx is a promising disease-modifying treatment for Huntington's disease (HD). Another study concluded a novel mechanism (ABX-1431) holds promise for the treatment of movement disorders and neuropsychiatric conditions. A third was the first ever pluripotent stem cell-based therapy for Parkinson's disease (PD) performed in humans, with promising results.

Huntingtin-lowering trial

In a phase 1/2a trial in patients with early stage HD, IONIS-HTTRx delivered via intrathecal injection was well tolerated with no drug-related adverse safety signals during the treatment or follow-up periods. Significant dose-dependent reductions in cerebrospinal fluid (CSF) mutant huntingtin (mHTT) were observed [1]. IONIS-HTTRx is an antisense oligonucleotide (ASO) designed to target huntingtin (HTT) mRNA. It is the result of a comprehensive drug discovery effort to design a well-tolerated ASO with high specificity to human HTT mRNA that potently suppresses HTT production. This preclinical stage took 10 years. In the first-ever drug trial to try to lower HTT, 46 patients were randomised (3:1) to receive 4 doses of IONIS-HTTRx or placebo by monthly bolus intrathecal injection, followed by a 4-month untreated period. Five ascending-dose cohorts were enrolled. IONIS-HTTRx was well tolerated at all doses. Adverse events were mostly mild and unrelated to study drug. There were no adverse trends in laboratory parameters. ASO was measurable in CSF and plasma, and concentrations were generally aligned with predictions from a linked PK/PD preclinical model. Significant, dose-dependent reductions in CSF mHTT were observed. In 23 out of 34 patients (68%) assigned to IONIS-HTTRx (RG6042), mHTT declined at last trough measurement (Figure 1).

Figure 1 mHTT protein (in CSF) percent change from baseline at study endpoint*



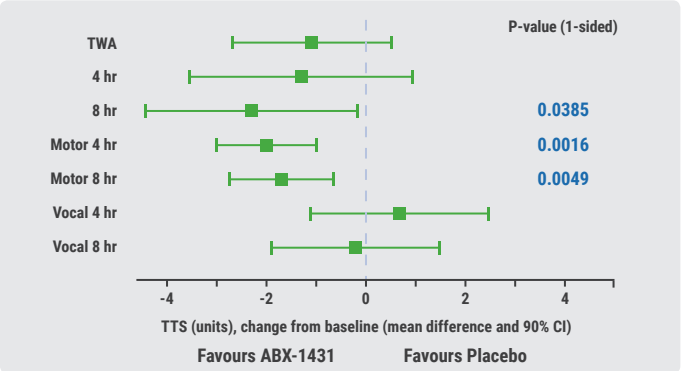
*Endpoint is defined as the later of Day 85 and 113

Novel mechanism to treat movement disorders

Modulation of the endocannabinoid system by selective inhibition of the enzyme monoacylglycerol lipase (MGLL) improves tics in Tourette Syndrome (TS). This was demonstrated by the trial results of ABX-1431, a first-in-class, oral, highly selective MGLL inhibitor. It raises nervous system concentrations of the endocannabinoid 2-AG, which acts as an agonist on presynaptic central cannabinoid receptors [2].

In a single-dose crossover study, 20 adult patients with moderate to severe TS were treated with 40 mg ABX-1431 or a placebo. Patients displayed a placebo-adjusted ABX-1431-related tic improvement in the Yale Global Tic Severity Scale Total Tic Score (YGTSS-TTS) at 8 hours (P=0.0384), with improvement in motor tics at 4 hours (P=0.0016) and 8 hours (P=0.0049), and a reduction in self-reported tic intensity at 4 hours (P=0.0005) and 8 hours (P=0.0008) (Figure 2). An improvement in premonitory urges was observed at 4 hours (P=0.0369). The most common adverse events were

Figure 2 YGTSS - Total Tic Score; placebo-corrected change-from-baseline with 90% confidence interval [2]



headache, somnolence, and fatigue, which were resolved. According to the researchers, ABX-1431 holds promise as a novel mechanism to treat different movement disorders and neuropsychiatric conditions.

Stem cell therapy for Parkinson's disease

The preliminary results of a phase 1 study showed that transplantation of human parthenogenetic stem cell-derived neural stem cells (ISC-hpNSC®) is safe, well tolerated and can potentially benefit patients with advanced PD [3].

A total of 12 patients, divided into 3 cohorts of 4, were injected with 30, 50 or 70 million ISC-hpNSC cells. Patients received stereotactic bilateral injections of 7 cell deposits per hemisphere into the caudate nucleus, putamen and substantia nigra. Four patients of the first cohort and two patients of the second cohort have been successfully transplanted with 30 and 50 million ISC-hpNSC cells, respectively. No serious adverse events associated with ISC-hpNSC had been reported thus far. Six months post transplantation, patients of the first cohort had an average improvement of 53% in the Questionnaire for Impulsive-Compulsive Disorders, 35% in the Beck Depression Inventory, 25% in OFF-time, and 16% across the different dimensions of the PD Quality of Life Score-39.

Deep Brain Stimulation in Parkinson's disease with a new device

The results of the prospective, double-blinded INTREPID study demonstrate that the use of a multiple-source, constant-current, deep brain stimulation (DBS) system is safe and effective in the treatment of PD symptoms [4]. Subjects were implanted bilaterally in the subthalamic nucleus with a multiple-source, constant-current DBS System (Vercise System). Blinded subjects were randomised to either receive active vs control settings for a 12-week period. Following the blinded period, subjects received their best therapeutic settings. The study successfully met the primary endpoint (P<0.001) with a mean difference of 3.03 (± 4.2) hours from baseline to 12 weeks between the active and the control group in ON time, with no increase in antiparkinsonian medications. The study also met several secondary endpoints. The incidence of infection was 2.7% and of peri-operative intracranial haemorrhage was 1%.

Subcutaneous L-dopa/carbidopa

Continuous subcutaneous L-dopa/carbidopa (ND0612H) can provide important benefits for advanced Parkinson's disease patients. This was concluded from the evaluation of 2 dosing regimens of ND0612H [5]. Regimen-1 was a 24h infusion with 720/90 mg LD/CD; regimen-2 was a 14h 'waking-day' infusion with 538/68 mg LD/CD + morning oral LD/CD 150/15 mg. Primary endpoint was the change to day 28 in daily OFF-time.

Of the 38 randomised subjects, 33 (87%) completed the study. Regimen-1 met the primary endpoint, with a mean reduction in OFF-time of 2.8 hours (P=0.004); 8 of 19 (42%) subjects had a complete reduction in OFF-time to 0 hours. The proportion of subjects with full ON was significantly increased at 8am (P=0.02) and 9am (P=0.007). 'Good' ON-time also increased, by a mean of 3.7 h (P<0.001). In regimen-2, mean reduction in OFF time was 1.3 h, which was not significant. 'Good' ON-time increased by 2.8 hours (P=0.003). Both regimens were well tolerated. Most frequent adverse events were mild-moderate infusion-site reactions: nodules (47%), bruising (18%), and erythema (18%).

Inhaled levodopa

CVT-301 is an investigational therapy that delivers levodopa to the lungs, intended to treat OFF-period symptoms in PD. Results from a prospective study were positive. Improvements in unified Parkinson's disease rating scale-III (UPDRS-III) scores as well as patient-reported measures support the efficacy of up to 52 weeks of treatment with CVT-301 84 mg [6].

A total of 408 subjects were randomised 2:1 to CVT-301 84 mg or to an observational cohort receiving oral standard-of-care. Overall, the average daily number of CVT-301 doses was 2.3. Least squares mean changes in UPDRS-III scores from predose to 10, 20, 30, and 60 min postdose were consistent from week 4 (-5.7, -12.0, -15.5, -16.1, respectively) to week 52 (-5.0, -11.5, -15.3, -14.8). In this period, 80-86% achieved ON within 60 minutes and remained ON, and over 75% reported improvement in Global Impressions of Change. Reduction in total daily OFF time was consistent over 52 weeks: 1.32 - 1.42 hours.

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Multiple Sclerosis

New AAN guidelines on the use of disease-modifying therapies (DMTs) in patients with multiple sclerosis (MS) were presented at the AAN meeting and simultaneously published on 23 April in Neurology [1,2]. In the new guidelines, clinicians are urged to discuss the benefits and risks of DMTs at an early stage of the disease. The need for earlier intervention was also expressed at sessions covering progressive MS (PMS). In addition, some progress was made in studying interventions for primary and secondary progressive MS.

New guidelines advocate early intervention

The AAN guidelines are an update of the 2002 version, providing guidance on starting, switching, and stopping treatment of relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS), as well as patients with clinically isolated syndrome.

The new AAN guidelines present 30 recommendations: 17 on starting DMTs, 10 on switching therapy, and 3 on stopping therapy. One of the recommendations is for clinicians to discuss the benefits and risks of DMTs at an early stage of the disease: after a single clinical demyelinating event and 2 or more brain lesions characteristic of MS. "We found that for most people it is better to start taking MS drugs early on, rather than letting the disease run its course", explained Prof. R.A. Marrie (University of Manitoba, Canada). "In these guidelines, several drugs have moderate to strong evidence for slowing certain MS processes."

Recommendations on starting disease-modifying therapies

Some of the other recommendations on starting DMTs, plus the level of evidence (A, B or C), include:

- Clinicians must ascertain and incorporate/review preferences in terms of safety, route of administration, lifestyle, cost, efficacy, common AEs, and tolerability in the choice of DMT in people with MS being considered for DMT. Clinicians must engage in an ongoing dialogue regarding treatment decisions throughout the disease course with people with MS (Level A).
- Clinicians should evaluate barriers to adherence to DMT in people with MS. Clinicians should counsel on the importance of adherence to DMT when people with MS initiate DMTs (Level B).
- Clinicians should prescribe alemtuzumab, fingolimod, or natalizumab for people with highly active MS (Level B).
- Clinicians should offer ocrelizumab to people with PPMS who are likely to benefit from this therapy unless there are risks of treatment that outweigh the benefits (Level B).

Recommendations on switching and stopping disease-modifying therapies

Some of the recommendations on switching and stopping DMTs are the following:

- Clinicians should evaluate the degree of disease activity, adherence, AE profiles, and mechanism of action of DMTs when switching DMTs in people with MS with breakthrough disease activity during DMT use (Level B).
- Clinicians should inquire about medication AEs with people with MS who are taking a DMT and attempt to manage these AEs, as appropriate. Clinicians should discuss a medication switch with people with MS for whom these AEs negatively influence adherence (Level B).
- In people with RRMS who are stable on DMT and want to discontinue therapy, clinicians should counsel people regarding the need for ongoing follow-up and periodic re-evaluation of the decision to discontinue DMT. Clinicians should advocate that people with MS who are stable (that is, no relapses, no disability progression, stable imaging) on DMT should continue their current DMT unless the patient and physician decide a trial off therapy is warranted (Level B).
- Clinicians may advise discontinuation of DMT in people with SPMS who do not have ongoing relapses (or gadolinium-enhanced lesions on MRI activity) and have not been ambulatory (EDSS ≥7) for at least 2 years (Level C).

Progressive multiple sclerosis: starting and stopping treatment

Progressive multiple sclerosis (PMS) was extensively covered at MS sessions. "I am slightly worried about this focus", said Prof. F. Barkhof (VUmc, the Netherlands) at a session on progressive MS. He gave a lecture after being awarded the 2018 John Dystel Prize for Multiple Sclerosis Research

for pioneering the use of MRI to improve MS diagnosis and understanding of the disease. "MS progresses much earlier than is usually assumed, only we do not recognise this well."

A presentation in line with Barkhof's remarks, reported in a registry study assessing long-term effects of DMTs initiated early vs later in the disease course [3]. Patients who started treatment with DMT late had shorter time to reach EDSS 6, but the delay did not influence mortality. The Danish authors concluded that their results support use of early treatment.

When to start DMT is one question, when to stop is another. Therapy discontinuation in an ageing population is often recommended, but clear data supporting this are lacking. A stable disease course in patients with long disease duration does not protect against disability progression after treatment discontinuation, regardless of age, a study found [4]. The study followed 193 patients who stopped DMT across three time points (approximately 3.8 years). Of these patients, 135 (69.9%) were classified as stable prior to discontinuing treatment, 58 (30.1%) were not. The mean age was 50.4 years, with a disease duration of 17.1 years. Of the 135 stable patients, 48 (35.6%) worsened in EDSS scores after discontinuation: 34.1% in patients <55 years and 37.7% in patients ≥55 years. Only 10 (17.2%) patients who worsened prior to DMT discontinuation continued to progress further (P=0.011).

Trials of disease-modifying therapies in progressive multiple sclerosis

Some of the new data on different DMTs in PMS were the following:

- Results of the ARPEGGIO trial of oral laquinimod in primary-progressive MS (PPMS) were negative [5]. Eligible patients (n=374) were originally randomly assigned 1:1:1 to receive laquinimod 0.6 or 1.5 mg or placebo. The 1.5 mg dose was discontinued due to safety concerns. The 0.6 mg dose did not slow the rate of brain volume change or of disease progression after 48 weeks. However, a 60% reduction was observed in new T2 lesions in actively treated patients. Prof. G. Giovannoni (London, UK) said "important lessons" were learned about the design of neuroprotective trials in PPMS.
- In the EXPAND study, siponimod reduced the risk of confirmed disability progression (CDP) by 21-26% in a typical SPMS population [6]. Post-hoc analyses using 3 different methods to control for the confounding impact of on-study relapses showed a consistent impact of siponimod on the risk of confirmed disability progression (CDP) independent of relapses. "The outcomes of our analyses confirm an effect on CDP independent of prior relapses", said Prof. J. Kuhle (Basel, Switzerland), "and corroborates that siponimod is probably a useful treatment for SPMS." In relapsing and non-relapsing SPMS subgroups of EXPAND, siponimod demonstrated a significant and clinically meaningful positive effect on cognitive processing speed [7].
- Ibudilast was associated with a 48% reduction in the rate of brain atrophy progression (P=0.04) in primary or secondary PMS [8]. In the NN102 SPRINT trial, subjects were randomised to ibudilast up to 100 mg/day or matching placebo. In the mITT analysis, 244 subjects (96%) were included; 220 (86%) completed 96 weeks follow-up. The AEs reported more commonly (P<0.1) with ibudilast included gastrointestinal events, rash, depression, and fatigue. There was no significant difference in serious AEs or discontinuation rates between the groups. Ibudilast was associated with a 77-82% reduction in change in MTR (P=0.05), and a trend for improvement on transverse diffusivity (P=0.15). These results support further investigation of ibudilast as a potential treatment for progressive MS.

Natalizumab extended-interval dosing and PML risk

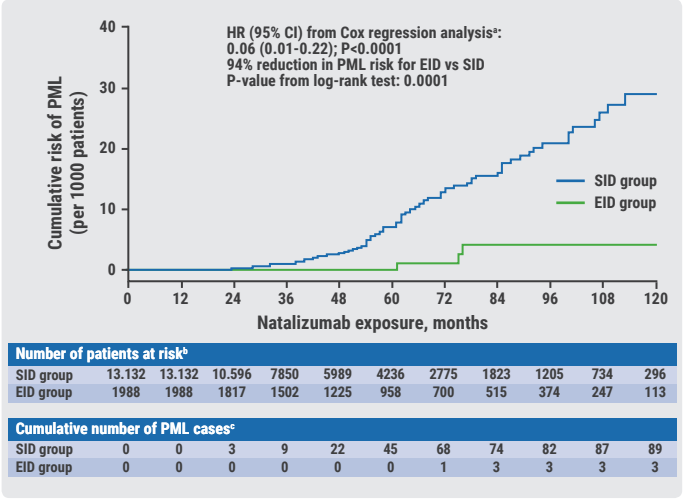
Natalizumab extended-interval dosing (EID) is associated with a highly significant lower risk of progressive multifocal leukoencephalopathy (PML) compared with standard-interval dosing (SID) in anti-JCV antibody positive patients [9]. The investigators used the following three approaches examining the effects of EID:

1. Primary definition: tests whether dosing history in the last 18 months of natalizumab treatment affects PML risk. EID was defined as ≤15 infusions in the last 18 months (540 days).
2. Secondary definition: tests whether an EID period occurring at any time in the dosing history affects PML risk.
3. Tertiary definition: tests whether a primarily EID dosing history affects PML risk.

The primary analysis included 15,120 patients (EID n=1,988; SID n=13,132) (Figure 1); the secondary 18,755 patients (EID n=3,331; SID n=15,424); and the tertiary analysis included 23,983 patients (EID n=815; SID 23,168). Most EID patients switched from SID to EID after >2 years of treatment.

In the first 4 years of treatment, only 1 PML case was observed for EID (with the secondary definition). In years 5

Figure 1 Gd+ lesions Kaplan Meier estimates of the cumulative probabilities of PML in EID versus SID groups; primary definition [9]



Number of patients at risk[b]											
SID group	13.132	13.132	10.596	7850	5989	4236	2775	1823	1205	734	296
EID group	1988	1988	1817	1502	1225	958	700	515	374	247	113

Cumulative number of PML cases[c]											
SID group	0	0	3	9	22	45	68	74	82	87	89
EID group	0	0	0	0	0	0	1	3	3	3	3

a) EID vs SID. Model includes age, gender, prior use of immunosuppressants, EID/SID group, and calendar year at the start of natalizumab treatment as covariates. b) Number of patients who were still in the study and did not have PML at the end of the specified time.
c) Cumulative number of PML cases at the end of the specified time.

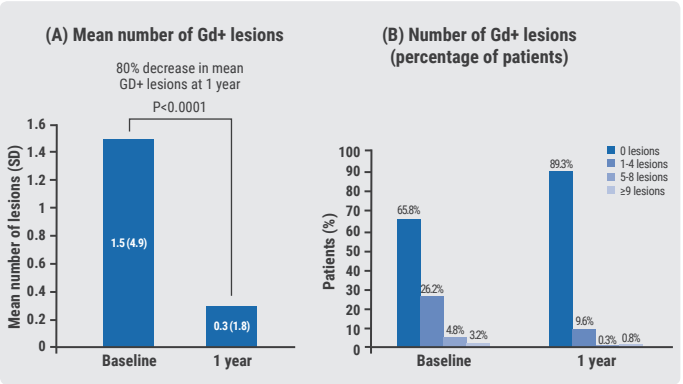
and 6, PML risk was substantially lower for EID than for SID across all 3 definitions. There was a 94% and 88% reduction in PML risk with EID vs SID in the primary and secondary analysis, respectively (both P<0.0001). As for the tertiary definition, there were no EID PML cases observed.

ALKS 8700 possible new option for relapsing-remitting multiple sclerosis patients

ALKS 8700 is a novel, oral prodrug of monomethyl fumarate in phase 3 development for the treatment of relapsing-remitting multiple sclerosis (RRMS). It was designed to treat MS with the same active metabolite as dimethyl fumarate but with potentially improved gastrointestinal tolerability. Preliminary findings from the EVOLVE-MS-1 study suggest ALKS 8700 may be an effective treatment option for patients with RRMS [10].

EVOLVE-MS-1 is a multi-centre, prospective, open-label, single-arm phase 3 study to assess long-term safety, tolerability, and treatment effect of ALKS 8700 462 mg twice daily in approximately 900 patients with RRMS. The 1-year MRI and relapse results for RRMS patients were reported. Annualised relapse rate (ARR) was 0.16 for the 570 patients (493.6 patient-years) evaluated during this interim analysis. Interim MRI results included 152 patients who completed MRI assessments at 1 year. Mean numbers of new/enlarging T2 lesions, gadolinium-enhancing (Gd+) lesions, and new T1-hypointense lesions were 2.8, 0.3, and 1.8, respectively. There was a significant reduction (P<0.0001) in the number of Gd+ lesions from baseline (mean 1.2) to 1 year (0.3) (Figure 2).

Figure 2 Gd+ lesions in de novo patients with a 1-year MRI assessment [10]



Gd+ = gadolinium-enhancing; MRI = magnetic resonance imaging; SD = standard deviation.

Fingolimod vs interferon β-1a in paediatric multiple sclerosis

Fingolimod was associated with consistent control of disease activity in paediatric MS across sensitivity/supportive analyses of the PARADIGMS trial. Benefits on disability progression were observed over the treatment duration of up to 2 years [11]. PARADIGMS was a double-blind phase 3 trial of 215 paediatric MS patients (age 10-18) in which fingolimod was compared to interferon (IFN) β-1a [12]. Administered up to 2 years, fingolimod significantly reduced annualised relapse rate (ARR) as well as the rate of new/newly enlarged (n/ne) T2 lesions.

In this new analysis, IFN neutralising antibody-positive IFN β-1a patients (n=9) were excluded; this did not have any tangible impact on the primary and key secondary results (81.5% ARR reduction and 47.6% reduction in n/ne T2 lesions, both P<0.001, vs 81.9% and 52.6% in the overall population, respectively). An additional analysis of participants who were treatment naïve (63.3%) revealed that the efficacy of fingolimod is this subpopulation (85.8% ARR reduction and 53.4% n/ne T2 lesion reduction vs IFN β-1a, both P<0.001) was also consistent with the overall population. The estimated percentage of patients without confirmed disability progression after 3 months up to 2 years was higher in the fingolimod group (95.2%) than in the IFN β-1a group (84.7%) (P=0.015), with a risk reduction of 77.2% (P=0.007).

Stem cell transplantation in rapidly evolving severe multiple sclerosis

Autologous haematopoietic stem cell transplantation (AHSCT) is a very effective treatment in patients with highly active relapsing-remitting multiple sclerosis (RRMS) who failed to respond to standard DMTs [13]. AHSCT also seems

to be safe and effective in treatment of naïve patients with rapidly evolving severe multiple sclerosis (RESMS). Seven RESMS patients with poor prognosis and median pre-treatment EDSS score of 5.5 received AHSCT in a single academic centre. The median follow-up was 18 (3-36) months and the median EDSS at the last follow up was 3 (2.5-6.5). No relapses were observed post-AHSCT. Only a single new Gd+ lesion was observed in 1 patient, 6 months after treatment. No common toxicity criteria grade 3 or 4 toxicities were observed and there was no treatment-related mortality.

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Neuromuscular Disorders

With the first-ever approved drug (eculizumab) to treat generalised myasthenia gravis (gMG), only approved by the FDA since October 2017, more therapies are welcome and may be on their way. Efgartigimod and RA101495 may be among them. Positive trial results were also reported on treatments of, among others, Duchenne muscular dystrophy, spinal muscular atrophy, and ALS.

New therapies for myasthenia gravis

Efgartigimod resulted in more clinical improvement in patients with myasthenia gravis (MG) than placebo through the entire duration of an 11-week proof-of-concept study [1]. Efgartigimod (ARGX-113) belongs to a new class of antagonists of the neonatal Fc receptor for Immunoglobulin G (IgG). ARGX-113 targets and binds this receptor, blocking the recycling of IgG and thereby eliminating IgG antibodies. The placebo-controlled study had 24 participants. "Efgartigimod resulted in rapid and sustained IgG reduction", said Dr J.F. Howard (UNC School of Medicine, USA). "75% achieved a lasting response of at least 6 weeks, vs 25% in the placebo group." Clinical benefit maximised 1 week after administration of the last dose, achieving statistical significance over the placebo group (P=0.0356) on the MG activity of daily living score. "Despite the huge placebo response, the between-group difference was very substantial."

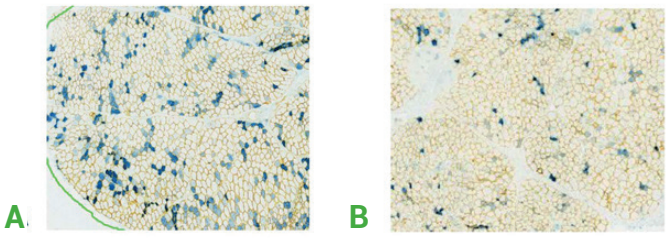
Positive results of a phase 1 study support further evaluation of RA101495 in a phase 2 study [2]. RA101495 is a peptide inhibitor of complement component 5 (C5). As the authors conclude, subcutaneous self-administration of RA101495 may not only enable a broader population of generalised MG patients to potentially benefit from targeted C5 inhibitor therapy, but also ease the treatment-related burden of intravenous options.

In patients with acetylcholine receptor antibody-positive generalised MG, rituximab was not effective for reducing the amount of steroids needed compared with placebo, according to the BeatMG phase 2 trial [3]. The primary outcome of the study was a ≥75% reduction in the average daily dose of prednisone 4 - 52 weeks after treatment. The mean reduction in the active and control group was 60% and 56%, respectively.

Duchenne muscular dystrophy

Interim results of a phase 2 open-label study of ezutromid supported the utrophin hypothesis and the potential for universal treatment for Duchenne muscular dystrophy (DMD) [4]. Ezutromid is a first-in-class utrophin modulator. Utrophin is a naturally occurring protein that may act as a functional replacement for dystrophin. Continuous expression in mature muscle fibres could modify the course of DMD. Ezutromid was administered to 40 ambulatory DMD patients. Primary endpoints were MRS assessments after 48 weeks. A significant reduction (of 11.37% to 8.76%) in fibres expressing developmental myosin heavy chain (MHCd) was observed (Figure 1). Decreased MHCd, a marker

Figure 1 Images showing MHCd staining in skeletal muscle biopsy from one patient (A) at baseline, (B) at 24 weeks; blue = positive [4]



of regeneration, indicates reduction in muscle damage. Utrophin levels were maintained and even increased, which, together with decreasing MHCd, provides evidence of target engagement.

Another study reported that the phosphorodiamidate morpholino oligomer (PMO) golodirsen increased exon 53 skipping, dystrophin production, and dystrophin sarcolemma localisation in all 25 patients that were analysed [5]. These patients are participants in an ongoing trial of golodirsen. This is the second PMO shown to increase dystrophin expression and membrane localisation through the initiation of exon skipping, further strengthening the potential utility of the PMO technology platform in DMD.

Spinal muscular atrophy

Interim survival motor neuron (SMN) protein data from FIREFISH Part 1 were presented for the first time [6]. FIREFISH is a multi-centre, open-label, seamless study of RG7916 in babies aged 1–7 months with type 1 spinal muscular atrophy (SMA) and two SMN2 gene copies. A dose-dependent increase in SMN protein levels in blood was observed, with an up to 6.5-fold increase vs baseline after 4 weeks of treatment at the highest dose of RG7916 (range 2.0 – 6.5). No safety-related stopping rules had been met, and while follow up was limited, no patient had lost the ability to swallow, had required tracheostomy, or had reached permanent ventilation. The observed increase in SMN protein compared favourably with the approximately 2-fold difference in SMN protein levels between SMA severity types (e.g. type 2 vs type 1). All doses explored so far have been well tolerated. FIREFISH is currently recruiting globally.

Also presented were interim results from the SHINE study of nusinersen for 89 patients with infantile-onset SMA (most likely to develop type 1) who transitioned from ENDEAR [7]. The results suggested longer-term treatment with nusinersen is still safe as well as effective. Participants who received intrathecal nusinersen in both ENDEAR and SHINE have continued improvements in motor function, such as sitting and head control, and in event-free survival time. Mean event-free survival time was also significantly longer for patients who received nusinersen in both trials compared to those who underwent a sham procedure in ENDEAR and then initiated nusinersen treatment in SHINE (73 and 23 weeks, respectively). There were no treatment-related serious adverse events.

Autologous stem cell transplantation in ALS

NurOwn® is an autologous adult stem cell therapy technology that uses bone marrow-derived mesenchymal stem cells (MSC), which are induced to secrete high levels of neurotrophic factors (NTFs). The improvements observed in a placebo-controlled study following MSC-NTF transplantation were reflected in all 4 domains of the revised ALS Functional Rating Scale (ALSFRS-R), particularly in the bulbar and fine motor subscales [8]. The 48 ALS participants were randomised 3:1 to active treatment or placebo and were followed for 6 months post transplantation. The primary safety endpoint was met. As for efficacy, a higher percentage of participants achieved ≥1.5 points/month improvement in the treated group at all time points. The percentage of responders (≥0.375 points/month improvement) in the ALSFRS-R bulbar domain (excluding slow progressors) was significantly higher in the treated group at 4, 8, 12, and 16 weeks (at all timepoints between 40-47% vs 0%). The percentage of responders in the ALSFRS-R fine motor domain (excluding slow progressors) was significantly higher in the treated group at 2 weeks: 87% vs 40%, one-sided (P=0.07).

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Stroke

"Acute stroke care will never be the same again", said Dr N. Rost (Mass General Hospital, USA), commenting on the huge importance and clinical implications of two recent randomised trials suggesting that the time window for mechanical thrombectomy may be further expanded in selected patients: to up to 16 hours according to the DEFUSE 3 trial, and up to 24 hours according to the DAWN trial.

Extended time window for thrombectomy

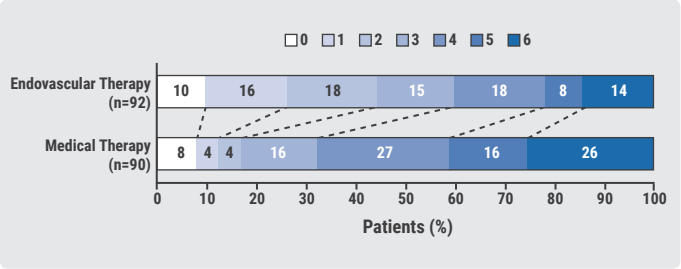
The results of the DAWN trial show the advantage of basing the decision to perform thrombectomy in patients with acute ischemic stroke on the presence of salvageable penumbral tissue rather than on a prespecified time window [1]. Thrombectomy performed between 6 and 24 hours after onset of acute stroke in patients with a mismatch between stroke symptoms and infarct volume resulted in better disability outcomes compared to standard care alone. No significant difference was found in AEs of intracranial haemorrhage and 90-day mortality.

The DEFUSE 3 trial confirmed the need to expand the time window for thrombectomy [2]. The conclusion was that endovascular thrombectomy for ischemic stroke 6 to 16 hours after presumed stroke onset plus standard medical therapy resulted in better functional outcomes than standard medical therapy alone among patients with proximal middle-cerebral-artery or internal-carotid-artery occlusion and a region of tissue that was ischemic but not yet infarcted.

Largest OR ever reported in a thrombectomy study

First author Dr G.W. Albers (Stanford University, USA) said the results were "quite striking". Median time between stroke onset and randomisation was almost 11 hours. Adding endovascular therapy to medical therapy was associated with a favourable shift in the distribution of functional outcomes on the modified Rankin scale at 90 days (OR 2.77; P<0.001) and a higher percentage of patients who were functionally independent, defined as a score on the modified Rankin scale of 0 to 2 (45% vs 17%, P<0.001) (Figure 1). Dr Albers: "This is the largest OR ever reported in a thrombectomy study." Indeed, the outcomes of the DAWN

Figure 1 Scores on the Modified Rankin Scale at 90 Days [2]



0 = no symptoms; 1 = no clinically significant disability; 2 = slight disability; 3 = moderate disability; 4 = moderately severe disability; 5 = severe disability; and 6 = death

and DEFUSE 3 trial are even better than of previous studies that adopted shorter intervention windows, suggesting the – still unexplained – presence of a late window paradox. The 90-day mortality rate was 14% in the endovascular-therapy group and 26% in the medical-therapy group (P=0.05). No significant difference was found between-group difference in the frequency of symptomatic intracranial haemorrhage (7% and 4%, respectively; P=0.75) or of serious AEs (43% and 53%, respectively; P=0.18).

The effect on clinical practice of the DAWN and the DEFUSE 3 trial was instant: new guidelines from the American Heart Association/American Stroke Association (AHA/ASA) recommend mechanical thrombectomy in eligible patients 6 to 16 hours after a stroke (level 1A). In view of the DAWN trial results, the procedure is considered "reasonable" 16 to 24 hours post-stroke (level 2a) [3].

Patent foramen ovale closure

Dr S.R. Messé (University of Pennsylvania, USA) dedicated his review of the past year to a single subject: that of patent foramen ovale (PFO) closure to reduce the risk of recurrent stroke. In the CLOSE trial, the rate of stroke recurrence was lower when PFO closure was added to antiplatelet therapy among patients who had had a recent cryptogenic stroke attributed to PFO with an associated atrial septal aneurysm or large interatrial shunt [4]. In the DEFENSE-PFO trial, PFO closure in patients with high-risk PFO characteristics resulted in a lower rate of the primary endpoint (a composite of stroke, vascular death, or thrombolysis in myocardial infarction [TIMI]-defined major bleeding) as well as stroke

recurrence during 2 years of follow up [5]. Dr Messé: "The real question is: which patients does PFO closure benefit?" He concluded PFO closure reduced stroke risk in patients with likely PFO-related stroke and the following characteristics:

- under 60 years of age, no other cause;
- embolic appearing stroke;
- few vascular risk factors;
- large shunt;
- atrial septal aneurysm.

In other patients with PFO, the benefits are uncertain. It is also not clear if closure benefits patients who require anticoagulation.

Protective effect of obesity

From an 11-year nationwide cohort of patients with ischemic strokes, a significant protective effect of obesity and better prognosis, including a lower mortality rate, was observed [6]. From 2003-2013, the American researchers identified 1,168,847 patients discharged with ischemic stroke as a primary diagnosis. Of these, 8.7% were found to be obese. Obese patients with ischemic stroke were more often younger, female, and African American as compared to Caucasian. After risk adjustment for demographics, and baseline comorbidities, obese patients with ischemic stroke had lower observed in-hospital mortality compared with non-obese patients with ischemic stroke: 2.5% vs 4%, OR: 0.717 (P<0.001).

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