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PEER-REVIEWED CONFERENCE REPORT

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Editor Prof. dr. Nikolaos Grigoriadis, AHEPA University Hospital, Thessaloniki, Greece

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Letter from the Editor

Prof. dr. Nikolaos Grigoriadis

Dear Reader,

A whole spectrum of neurological disorder studies was represented in the AAN, 21-27 April 2017, Boston. This newsletter compiles a number of studies related to risk-factor identification, clinical trials, pivotal clinical trial extension, real world data, innovative therapeutic approaches, presented in this meeting. The effect of intensive reduction of systolic blood pressure (BP) on hematoma expansion after intra-cerebral haemorrhage (ICH), were discussed. The identification of BP as the most important risk factor contributing to stroke and dementia, the potential ineffectiveness of cholinesterase inhibitors in mild cognitive impairment, the new guidelines on Sudden Unexpected Death in Epilepsy, the cannabidiol use for epilepsy, were presented. Immune therapies in migraine, the use of extended-release carbidopa-levodopa, subcutaneous apomorphine, and gene therapy in PD, were also presented. MS – related studies were impressively many. Among them, the use of autologous EBV-specific T-cells in PPMS, the con-current use of opicinumab and (IFN) beta-1a, im, in active RRMS or SPMS, the robust effects siponimod in SPMS, the use of dimethyl fumarate (DMF) in paediatric MS, data from the extension studies of Alemtuzumab, the rapid effect of ocrelizumab and the efficacy of cladribine tablets, were among the most spectacular news at 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 in the same institution. He has been specialized in clinical and experimental Neuroimmunology and CNS immunopathology in a number of research centers and institutions abroad. He is now Professor of Neurology and Head of the of the B' Dept of Neurology, AHEPA University Hospital, the MS Centre and the Laboratory of Experimental Neurology and Neuroimmunology. Professor 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), Co-founder and Secretary of the Hellenic Academy of Neuroimmunology. He is Ad Hoc reviewer in international scientific journals, co-ordinator in more than 40 multicenter clinical trials for MS and principal investigator in collaborative research projects for cell therapies in CNS autoimmune demyelination. His field of interests are: neuroimmunology; multiple sclerosis; experimental models of autoimmune diseases (EAE etc); neurodegeneration; immunomo-dulation; cell therapies. He has published more than 150 papers in peer reviewed journals.

Cerebrovascular Disease and Intravenous Neurology

A much-discussed trial was ATACH 2: intensive reduction of systolic BP after ICH did not reduce hematoma expansion as much as expected; perhaps because the control group was treated 'too well'? Slightly counter-intuitive' was the finding that oral anticoagulation treatment (OAT) was associated with decreased mortality and favourable outcome after both non-lobar and lobar ICH.

Intensive blood pressure reduction in intra-cerebral haemorrhages

Compared with standard reduction, intensive reduction of systolic BP appeared to reduce hematoma expansion in patients with ICH with initial hematoma volume ≥10 ml in a randomised study [1]. Hematoma enlargement was a significant predictor of death or disability in this patient cohort. A total of 876 subjects were randomised to intensive-treatment (goal <140 mmHg) or standard-treatment (goal <180 mmHg, but ≥140 mmHg) within 4.5 hours of symptom onset. For intensive and standard treatment groups, the proportion of subjects with any hematoma expansion was 46.4% and 52.3%, respectively (response rate 0.89). The proportion of subjects with hematoma expansion (>33% increase) was 18.9% and 24.4%, respectively (response rate 0.77). In subjects with initial hematoma volume ≥10 ml (n=438), any hematoma expansion was seen in 53.8% and 61.3% (response rate 0.88), and hematoma expansion (>33% increase) in 18.6% and 27.6% (response rate 0.67). Hematoma enlargement was significantly associated with death or disability at 3 months post-randomization (response rate 1.59).

The lack of more distinct between-group differences may be explained by the fact that almost all participants reached a systolic-BP <140 mmHg, Goldstein commented. "Treatment doses seem to have been too high to properly verify our hypothesis." He added that a post-hoc secondary analysis suggests that bouncing back to higher BP-levels (which occurred in 31.6%) after intensive BP-lowering seems to result in relatively unfavourable outcomes.

Resuming anticoagulation after intra-cerebral haemorrhages

"Whether or not to resume oral anticoagulation after intracerebral haemorrhage is one of the most vexing questions in ICH-care", said Dr. A. Biffi from Boston. He presented the results from a study that found resumption of OAT to be associated with decreased mortality and favourable outcome after both non-lobar and lobar ICH [2]. Biffi and colleagues explored the impact of ICH location – the primary determinant of re-bleeding risk – on functional outcome after OAT resumption. They meta-analysed 3 large-scale trials: RETRACE, MGH and ERICH, including 641 non-lobar OAT-ICH and 386 lobar OAT-ICH survivors. Among non-lobar and lobar ICH survivors 179/641 (28%) and 88/386 (23%) resumed OAT, respectively.

Discharge modified ranking scale was associated with OAT resumption in lobar ICH only (OAT: median 3.5; no OAT: median 4.0; P=0.011). OAT resumption after non-lobar ICH was associated with decreased mortality: hazard ratio (HR) =0.22 (P<0.0001) and improved functional outcome: HR=5.12 (P<0.0001) at one year. OAT resumption after lobar ICH was also associated with decreased mortality: HR=0.25 (P<0.0001) and favourable functional outcome: HR=4.89 (P<0.0001). Dr. D.F. Hanley from Baltimore said the results were "somewhat counter-intuitive". He stressed that event rates (after only one year) were low, and that population studies are needed to find more definitive answers.

Intravenous-glyburide: edema-related endpoints

Two post-hoc analyses of results of the phase 2 GAMES-RP trial of intravenous-glyburide in patients with large hemispheric infarction were presented [3,4]. They provide supporting evidence that intravenous-glyburide may reduce edema-related deaths, but not malignant edema defined as an increase of ≥4 points in the NIHSS score.

In GAMES-RP patients aged 18 to 80 years with baseline large stroke lesions were randomised 1:1 to intravenous-glyburide or placebo. The adjudication outcomes were mortality due to all causes, and death due to cerebral edema. Results showed

that subjects treated with intravenous-glyburide had a trend toward lower all-cause mortality at one year (weighted log-rank test, P=0.052). The active treatment reduced the proportion of deaths due to cerebral edema: 2.4% with intravenous-glyburide vs. 22.2% with placebo (P=0.007). The frequency of parenchymal hematoma was not statistically different; the incidence of malignant edema was also similar. Another post-hoc analysis suggests that patients under 70, who may be at highest risk for poor outcomes secondary to edema after large hemispheric infarction, may have improved survival, better functional outcome and improved quality of life following treatment with intravenous-glyburide [4]. Mortality at 12 months was lower in the intravenous-glyburide group: 14% vs. 40% (odds ratio (OR) 4.00; P=0.025). There was a trend towards improved functional outcome in these patients (OR 2.24; P=0.080), higher score on the Barthel Index (BI) (mean 60.1; P=0.03), and higher score on the EuroQol 5 dimensions questionnaire (EQ-5D) (mean 0.49; P=0.04).

In short

- Thrombectomy for acute ischemic stroke patients due to emergent large vessel occlusion of the middle cerebral artery M2 segment with Stent-retriever appears to be feasible, with a significantly higher rate of recanalization, lower symptomatic intracerebral haemorrhage rate, and favourable 90-day modified ranking scale compared to aspiration and Mechanical Embolus Removal in Cerebral Ischemia [5].
- BP does not affect the benefit or safety of intra-arterial treatment in patients with acute ischemic stroke caused by proximal intracranial vessel occlusion [6]. These data from a post-hoc analysis of the MR CLEAN study provide no arguments to withhold or delay intra-arterial treatment based on BP.
- Oral anticoagulation and prolonged international normalization ratio is significantly associated with primary interventricular haemorrhage in a single-centre retrospective study [7].
- Aspirin appears to decrease the severity of AIS in a dose-response fashion. The effect of aspirin in the acetylation of albumin could not be observed [8]. Acetylation of additional proteins will be studied in an attempt to identify patients who respond best to aspirin.

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Dementia, Behavioural and Cognitive Neurology

Hypertension is the most important modifiable risk factor for cerebrovascular pathology contributing to stroke and dementia. Surprisingly, lowering of BP in older adults with borderline hypertension may be harmful to cognition. Another somewhat surprising finding was that cholinesterase inhibitors (ChEIs), approved for Alzheimer disease (AD), may not be effective in mild cognitive impairment (MCI).

Hypertension and risk of dementia

Elevated BP in mid-life (40–64 years), persistent hypertension into late-life (≥65 years), but also a steep decline in BP from mid-to-late life among non-hypertensives, were associated with an elevated risk of dementia in a community-based sample [1]. This sample consisted of 1440 dementia-free participants from the Framingham Heart Study, who had attended 5 consecutive quadrennial examinations between 1983 and 2001. They have been rigorously followed since

for incident dementia. During a mean follow-up of 8 years, 107 participants developed dementia. Mid-life systolic hypertension (≥140/90 mmHg) was independently associated with an increased risk of incident dementia: HR 1.57 (95% CI, 1.05–2.35). The same was true for persistent systolic hypertension into late-life: HR 1.96 (95% CI, 1.25–3.09). Among individuals with low to normal midlife BPs (≤140/90 mmHg), a steeper than average decline in systolic BP from mid-to-late life was also associated with an increased risk of dementia: HR 2.40 (95% CI, 1.39–4.15). These data highlight the potential sustained cognitive benefits of lower midlife BPs. However, lowering of BP in older adults with borderline hypertension may be harmful to cognition, despite a beneficial impact on cardiovascular events.

Cholinesterase inhibitors in mild cognitive impairment

No less unexpected were the outcomes of the efficacy of ChEIs in MCI. A study of 2,264 participants suggests that ChEIs may not improve the overall course in individuals with MCI due to AD (MCI-AD) or mild AD dementia (ADdem) [2].

35% of 966 MCI-AD and 72% of 1,298 ADdem participants in this American cohort were ChEI users. In both groups, ChEI users had higher education, were less often African American/other race, and more often had an APOE e4 allele (P<0.05). Cognitive decline was significantly steeper at ChEI initiation than before initiation in both groups (e.g., CDR-SB change in MCI-AD: 0.03 points/year before initiation, 0.85 points/year after initiation). Over the entire UDS follow-up, ChEI users in both the MCIAD and ADdem groups had a significantly faster cognitive decline compared to non-users (e.g., CDR-SB change in MCI-AD: 0.70 points/year among ChEI users, 0.21 points/year among non-users). The authors conclude that ChEI prescription and use in patients with MCI-AD or ADdem may not improve the overall course. They added that the faster decline in ChEI users after ChEI initiation may imply the expected decline that prompted ChEI use in the first place.

Monoclonal antibody for progressive supranuclear palsy in Alzheimer's disease

The results of a double-blind, placebo controlled phase 1 study of ABBV-8E12 in patients with progressive supranuclear palsy (PSP) were presented. ABBV-8E12 is a humanised anti-tau monoclonal antibody in development for the treatment of PSP and Alzheimer's disease (AD). When administered as a single dose up to 50 mg/kg in PSP patients, ABBV-8E12 had an acceptable safety and tolerability profile, which supports repeat-dose testing in patients with tauopathies [3].

A total of 30 patients were enrolled, with a mean age of 69.4 years and a mean PSP rating scale score of 35.6. They were randomized 3:1 to drug or placebo and received an intravenous dose of ABBV-8E12 (2.5, 7.5, 15, 25, 50 mg/kg) or placebo. A total of 27 patients completed the 84-day follow-up; 1 (3.3%) patient withdrew from the study due to adverse events (AEs). AEs occurred in 21 of 30 (70%) participants. AEs with the highest incidence were dermatitis (n=5) and fall (n=5). Dose-proportional increases in AUC and Cmax were observed.

DM/Q for pseudobulbar affect

Dextromethorphan hydrobromide/quinidine sulphate (DM/Q) showed persistent efficacy in treating pseudobulbar affect (PBA) throughout 24 weeks of double-blind and open-label treatment [4]. DM/Q 20/10 mg twice daily is still the only FDA-approved treatment of PBA. It was also approved by the European Medicines Agency (EMA), but is not available in Europe. Results of a 12-week open-label extension (OLE) of a phase 3 trial to evaluate persistence of its effect in PBA secondary to amyotrophic lateral sclerosis or multiple sclerosis were presented. In the original 12-week, double-blind trial, patients received placebo, DM/Q 20/10 mg, or DM/Q 30/10 mg twice daily; during OLE, patients received DM/Q 30/10 mg twice daily. Center for Neurologic Study-Lability Scale (CNS-LS) scores were measured at all clinic visits. Of 253 enrolled OLE patients, 92.9% completed the study; 4% discontinued for AEs. Regardless of double-blind treatment assignment, PBA symptoms significantly improved from baseline. CNS-LS mean score was 20.4 throughout the OLE. Mean CNS-LS changes from double-blind baseline to each OLE visit (after 15, 42, and 84 days) were −9.4, −9.3, and −9.2, respectively (all P<0.001). The 52 patients with a >48-hour gap in DM/Q treatment between DB and OLE had a significant return of PBA symptoms while off treatment: mean CNS-LS increased by 4.5 (P<0.001).

Since many autistic adults may have similar irritability as PBA patients, DM/Q was also evaluated in adult autistic patients with frontal lobe pseudobulbar irritability. A placebo-controlled study showed significant improvement in 13 autistic patients [5]. All primary and secondary standardised scales were statistically significant for improvement of irritability and function with DM/Q over placebo.

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Epilepsy

Important news at the AAN meeting in Boston was the presentation and simultaneous publication [1] of new guidelines on Sudden Unexpected Death in Epilepsy (SUDEP). Patients see it as their right to be informed on this delicate issue. There is a growing body of evidence that supports cannabidiol use for epilepsy and related syndromes, as illustrated by 2 trials highlighted in this report. Other studies highlighted here concern very difficult to treat subpopulations of epilepsy patients.

New guidelines on SUDEP

The AAN and the American Epilepsy Society have co-developed new guidelines on SUDEP, endorsed by the International Child Neurology Association. "It is important that the rate of occurrence of SUDEP and the specific risk factors are communicated to persons and families affected by epilepsy," commented first author Cynthia Harden from New York. "Our guideline brings clarity to the discussion, giving health care providers practical information they can use to help people with epilepsy reduce their risk."

The authors performed a systematic review of evidence. Based on 12 class 1 studies, they found that SUDEP typically affects 1 in 1,000 adults every year, and 1 in 4,500 children. When informing their patients or parents/guardians, clinicians should stress that 999 of 1,000 adults and 4,499 of 4,500 children are not affected. The major risk factor for SUDEP are generalised tonic-clonic seizures (GTCS); the SUDEP risk increases in association with increasing frequency of GTCS occurrence (Table 1). Healthcare professionals should inform their patients that seizure freedom, particularly freedom from GTCS, is strongly associated with decreased SUDEP risk.

Whether or not to discuss SUDEP with patients and families has created much debate. What do patients themselves think? Results of a questionnaire, completed by 42 adult epilepsy patients and caregivers, revealed that 100% of patients felt it is their right to be informed about SUDEP, while 92% felt that healthcare professionals should be required to inform patients [2]. Respondents agreed that SUDEP awareness motivated them for better medication adherence (81%) and management of their seizure triggers (85%). 30% endorsed increased fear, with a trend (P=0.08) to be more prevalent in the GTCS group.

Cannabidiol in two syndromes

Cannabidiol add-on therapy for the treatment of drop seizures associated with lennox-gastaut syndrome may be efficacious, 2 controlled trials of cannabidiol oral solution suggest: GWPCARE3 and GWPCARE4 [3,4]. Cannabidiol was generally well-tolerated.

In GWPCARE3, eligible patients were 2–55 years old (mean age 16 years), had ≥8 drop seizures during 4-week baseline, and had failed on ≥1 antiepileptic drug. A total of 225 participants were randomised to cannabidiol 20 mg/kg/day, cannabidiol 10 mg/kg/day, or placebo for 14 weeks. Reduction in drop seizure frequency over the 14-week treatment was significantly greater for cannabidiol 20 mg/kg (42%) and 10 mg/kg (37%) than placebo (17%; P=0.0047 and P=0.0016). AEs occurred in 94%, 84% and 72%, respectively, mostly mild or moderate. The most common AEs were somnolence and decreased appetite. Treatment-related serious AEs were reported in 5, 2 and 0 patients, respectively.

In GWPCARE4, 171 lennox-gastaut syndrome patients were randomised to cannabidiol 10 mg/kg/day or placebo. Efficacy and safety outcomes were similar. Cannabidiol resulted in a significantly greater reduction in monthly drop seizure frequency vs. placebo: 44% vs. 22% (P=0.0135).

Cannabidiol was also studied as a treatment of convulsive seizures in children with dravet syndrome. A double-blind randomised controlled trial (RCT) provides class A, level 1 evidence to support the use of pharmaceutically-produced cannabidiol for this indication [5]. The trial randomised 120 children and adolescents with Dravet syndrome and drug-

Table 1 Conclusions for sudden unexpected death in epilepsy (SUDEP) risk factors

Factor	OR (CI)	Confidence level
Presence of GTCS vs lack of GTCS	10 (17-14)	Moderate
Frequency of GTCS	OR 5.07 (2.94-8.76) for 1-2 GTCS per year and OR 15.46 (9.92-24.10) for >3 GTCS per year	High
Not being seizure-free for 1-5 y	4.7 (1.4-1.6)	Moderate
Not adding an AED when patients are medically refractory	6 (2-20)	Moderate
Noctural supervision (risk reduction)	0.4 (0.2-0.8)	Moderate
Use of noctural listening device (risk reduction)	0.1 (0-0.3)	Moderate

Abbreviations: AED = antiepileptic drug; CI = confidence interval; GTCS= generalized tonic-clonic seizure; OR = odds ratio

resistant seizures to receive cannabidiol oral solution up to 20 mg/kg/day, or placebo. Average monthly seizure frequency decreased from 12.4 to 5.9 in the cannabidiol-group, and from 14.9 to 14.1 in the placebo-group (a median reduction of 39% and 13%, respectively; P=0.012). Participants who received cannabidiol were nearly twice as likely to have at least a 50% reduction in convulsive seizure frequency: 42.6% vs. 27.1% (OR=2.0, P=0.078). There was no between-group difference in non-convulsive seizures. Serious AEs were reported more often in the cannabidiol-group than in the placebo-group: 16.4% vs. 5.1%. These included somnolence, fatigue, and elevated liver enzymes.

EPA and DHA in drug-resistant epilepsy

A double-blind RCT demonstrates that eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids are effective in reducing seizure frequency in drug-resistant epilepsy [6]. The researchers added that further, larger multi-centre studies are needed.

A double-blind RCT that was performed in Sundan included 99 drug-resistant epilepsy patients, aged 5 -16 (n=85) and 17- 45 (n=14). They were randomised to 2, 4 or 6 capsules of DHA (417.8 mg DHA and 50.8 mg EPA/capsule, n=33), EPA (385.6 mg EPA and 81.2 mg DHA/capsule, n=33) or matching placebo (n=33) for 1 year. A total of 59 patients (59.6%) completed the study. The average number of seizures per year were: EPA, 113.7, DHA, 145.5, and placebo, 182.8. Age, gender, and seizure type adjusted seizure incidence rate ratios of the EPA and DHA groups were 0.58 (P=0.009) and 0.61 (P= 0.01), respectively, compared to placebo. There was no difference in incidence rate ratio between the EPA and DHA groups (P=0.8). There were no treatment-emergent AEs (TEAEs).

Everolimus for tuberous sclerosis complex associated seizures

Reductions in treatment-refractory seizures associated with tuberous sclerosis complex (TSC) were sustained over time with adjunctive everolimus, as was shown in the extension phase of the EXIST-3 trial [7]. The safety profile was consistent with the core phase.

Epilepsy occurs in 85% of patients with TSC; ~60% become refractory to antiepileptic drugs. EXIST-3 demonstrated significantly reduced seizure frequency with everolimus vs. placebo in the 18-week core phase. In the extension phase, patients could receive everolimus (target exposure = 3-15 ng/mL) until ≥48 weeks. A total of 361 patients received everolimus in core or extension phases. Relapse rate at week 18 was 31%, vs. 46.6% at 1 year and 57.7% at 2 years. Greater benefit was observed in younger patients at 1 year of follow-up. Median PR in seizure frequency at week 18, at 1 year and at 2 years was 31.7%, 46.7% and 56.9%, respectively. A total of 95 patients discontinued everolimus before 2 years. Sensitivity analysis confirmed sustained benefit over time: relapse rate =30.2% at week 18 vs. 38.8% at 1 year and 41% at 2 years. AE emergence frequency did not increase over time (<6 months, 77.8%; 6-12 months, 46.2%; 2nd year, 45.5%). Grade 3/4 AEs occurred in 40.2% of patients. Forty-seven patients (13%) discontinued due to AEs.

Continuous cortical stimulation

Continuous subthreshold cortical stimulation may be a suitable treatment for focal epilepsy patients with lesions involving critical cortical areas or those with a localised seizure onset zone for whom a potentially reversible procedure is attractive [8]. The researches added that intracranial electroencephalography (iEEG) spike rate could be a useful biomarker for treatment efficacy.

The 13 participants had drug resistant epilepsy (DRE) and were deemed unsuitable for resective surgery. Cortical electrical stimulation was given via the surgically implanted subdural grid and depth electrodes used for iEEG monitoring. The mean decrease in disabling seizures was 80% (range 33-100%) following chronic stimulation. Out of 13 patients, 10 (77%) reported improvement for both epilepsy severity and life satisfaction. iEEG spike rates decreased significantly for all analysed patients. The mean spike rate decreased from 0.61 to 0.08 IED/s (P=0.002). The results of this trial were previously published in JAMA Neurology [9].

Does seizure activity have a rhythm?

Seizures and interictal epileptiform activity (IEA, a marker of brain irritability) are substantially influenced by underlying rhythms in long timescales: several days to weeks or more ("multidien") [10]. These multidien rhythms suggest underlying therapeutic endocrine or metabolic targets that deserve further study. The results also highlight opportunities to decrease refractory seizure burden through dynamic predictive therapeutic adjustments.

Recent quantitative analyses suggested that seizures may be temporally regulated over long timescales. The researchers quantified continuous IEA and seizure detection from 37 patients implanted intracranially for years with ambulatory electrocorticography. Results not only confirmed circadian distribution of IEA, but also suggest robust superimposed multidien rhythms. Cycle durations differed between patients and were stable over time, without any coherence with the lunar cycle. Seizures were phase-locked to the underlying multidien rhythms of IEA, occurring preferentially during the upslope of the period (P<0.05 for 13 out of 14 subjects).

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Migraine

Encouraging results were presented on a number of prophylactic and acute treatments of migraine. The most conspicuous were the very positive results of 2 CGRP receptor monoclonal antibodies, most notably of erenumab. CGRP is involved in the pathophysiology of migraine; antagonists of CGRP may have a pivotal role in preventing chronic migraine. A very important finding was the lack of AEs. Another noteworthy trial was CHAMP, which revealed that both amitriptyline and topiramate are no more effective than placebo in childhood migraine.

Prophylaxis with erenumab

Treatment with erenumab (AMG 334) can reduce the frequency of episodic migraine, findings from 2 phase 3 RCTs suggest, STRIVE and ARISE [1,2]. The safety/tolerability profile was similar to placebo. Both trials evaluated erenumab as a prophylactic treatment for episodic migraine.

In the STRIVE trial, 577 adult patients were randomised to subcutaneous, monthly erenumab 70 mg or placebo. Primary endpoint was change in monthly migraine days (MMDs) in a 12-week double-blind phase. At baseline the MMD was a mean 8.3. The erenumab and placebo groups experienced a mean 2.9- and 1.8-day reduction in MMDs, respectively (P<0.001). Monthly acute migraine-specific medication use was reduced by mean -1.2 and -0.6 days (P=0.002). Respective ≥5-point improvement in physical impairment (PI) was achieved by 33% and 27% of patients (P=0.13). The safety profile of erenumab was similar to placebo.

In the ARISE trial, 955 adult patients were randomised to erenumab 70 mg, 140 mg or placebo for 24 weeks. The mean MMDs at baseline was 8.3. Subjects experienced reductions of 3.2-, 3.7-, and 1.8-day, respectively (P<0.001 for both) over weeks 13-24. Monthly acute migraine-specific medication days were reduced by -1.1, -1.6, and -0.2 days (P<0.001). Subjects had improved PI and EA scores. Numerically greater efficacy was consistently observed for the 140 mg dose across all endpoints. Most frequently reported AEs across both groups were upper respiratory tract infection, injection site pain, nasopharyngitis, and sinusitis.

Another anti-CGRP antibody

Results of another anti-CGRP antibody (ALD403) were presented, for the prevention of chronic migraine [3]. The authors concluded that ALD403 100 mg and 300 mg significantly reduced migraine days in patients with chronic migraine as measured by 75% responder rates.

In this phase 2 trial patients with 15 to 28 headache days per month of which at least 8 were migraine days, were randomised to a single intravenous dose of ALD403 300 mg, 100 mg, 30 mg, 10 mg or placebo. The primary endpoint was a 75% reduction in migraine days per month from baseline to week 12. Of 662 patients randomised, 616 received treatment and 588 were included for efficacy. Baseline migraine days were between 16.2 and 16.5 days per month. 33% of patients had a 75% reduction in migraine days for the entire 12 weeks (P<0.05): 31% (P<0.05), 28%, 27% and 21% for ALD403 300 mg, 100 mg, 30 mg, 10 mg and placebo. In a post-hoc analysis, all doses of ALD403 significantly reduced the percentage of severe attacks. Relative to baseline, this

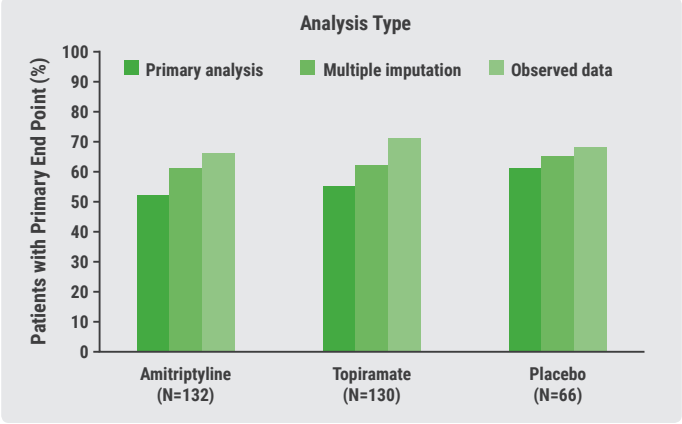
percentage decreased by 21% (P<0.005): by 16% (P<0.05), 18% (P<0.05), 16% (P<0.05), and 10% respectively. The infusion was well tolerated, with no serious drug-related AEs or infusion reactions identified.

Children are not little adults

One of the most interesting migraine-related trials presented was negative, but nonetheless has important implications for daily practice. The randomised, double-blind CHAMP trial revealed no significant differences in reduction in headache frequency or headache-related disability in childhood and adolescent migraine with amitriptyline, topiramate, or placebo over a period of 24 weeks [4].

The participants, 8-17 years of age, were randomised to amitriptyline (1 mg/kg/day), topiramate (2 mg/kg/day), or placebo. The primary outcome was a reduction of 50% or more in the number of headache days when comparing the 28-day baseline period with the last 28 days. A total of 328 participants were included in the primary efficacy analysis. The trial was concluded early for futility. There were no significant between-group differences in the primary outcome, which occurred in 52%, 55% and 61% of the patients in the amitriptyline, topiramate, and placebo group, respectively. There were also no significant between-group differences in headache-related disability, headache days, or the percentage of patients who completed the 24-week treatment period. AEs occurred more frequently in the amitriptyline or topiramate group compared to placebo, including fatigue (30% vs. 14%) and dry mouth (25% vs. 12%) in the amitriptyline group and paresthesia (31% vs. 8%) and weight loss (8% vs. 0%) in the topiramate group. A total of 3 patients in the amitriptyline group had serious AEs of altered mood. Over 90% of data on childhood migraine are derived from adult data, as was pointed out by Dr S. W. Powers (Cincinnati, US). "As this much needed trial clearly indicates, children are not little adults."

Figure 1 Patients with a Relative Reduction of 50% or More in the Number of Headache Days



Shown is the percentage of patients with a relative reduction of 50% or more in the number of headache days in the comparison of the 4-week baseline period with the last 4 weeks of a 24-week trial (primary end point). Results are shown for the primary analysis and two a priori sensitivity analyses to assess the effect of missing data. Sample sizes for the trial groups represent the primary analysis population. For observed data, the population is the subgroup with observed data at week 24.

OnabotulinumtoxinA

Results from a multicentre, open-label study COMPEL support the efficacy and safety of onabotulinumtoxinA for chronic migraine [5]. Progressive improvements in efficacy were observed through 108 weeks (9 treatment cycles), with no new safety issues.

A total of 716 patients were enrolled, who were treated with onabotulinumtoxinA 155U every 12 weeks. They were between 18–73 years of age, and primarily female (84.8%). The average number of headache days per month was 22.0 at baseline; pain was primarily characterised as throbbing/pulsing (70.8%). By 108 weeks, the number of headache days per month had decreased by 10.7 days (P<0.0001), with 75.0% of patients experiencing a ≥30% decrease in headache days from baseline. At 108 weeks, there was also a significant 7.1 point decrease in headache impact test (HIT-6) scores, and a 34.8 point decrease in Migraine Disability Assessment Questionnaire (MIDAS) (P<0.0001 for both). Domain scores of the Migraine Specific Quality of Life Questionnaire (MSQ) improved by 15.2, 22.3, and 22.1 points in role function preventive, role function restrictive, and emotional function subscales, respectively. A total of 131 patients (18.3%) reported ≥1 TRAE; neck pain (4.1%) was most frequently reported. Only 1 patient reported a serious TRAE: rash.

Non-invasive vagus nerve stimulation

Results of the ACT2 study evaluating non-invasive vagus nerve stimulation (nVNS) as acute treatment of cluster headache (CH) supports its use in patients with episodic CH, but not in chronic CH [6].

Adults with CH received nVNS or sham therapy during a 2-week double-blind period. At attack onset, subjects self-administered 3 consecutive 120-second stimulations to the

vagus nerve (cervical branch). If the attack was not aborted within 9 minutes, 3 additional stimulations were permitted. Efficacy was assessed after 15 minutes. The primary end point was the proportion of attacks that achieved pain-free status.

Efficacy evaluations included 48 nVNS-treated and 44 sham-treated subjects. In the total cohort, the primary end point did not differ significantly between treatments (nVNS, 14%; sham, 12%). In the episodic CH subgroup, nVNS (48%) was superior to sham (6%; P=0.01); the chronic CH subgroup showed no significant treatment difference. Proportions of subjects with responder status (pain score=0-1) for >50% of attacks were significantly higher with nVNS than with placebo in the total cohort: 40% vs. 14%.

Another poster reported on the experience in 2 London hospitals with non-invasive vagus nerve stimulation for treatment of indomethacin-sensitive trigeminal autonomic cephalalgias [7]. The initial results in 14 patients suggest it is effective for paroxysmal hemicrania and hemicrania continua, which may offer an indomethacin-sparing alternative for these conditions.

Transcranial magnetic stimulation

The open label ESPOUSE study suggests that single pulse transcranial magnetic stimulation may be an effective, well-tolerated treatment option for migraine prevention [8]. This acute treatment is FDA-approved for migraine with aura.

The study's treatment protocol consisted of both preventive treatment (4 pulses twice daily) and acute treatment (3 pulses at 15 minute intervals repeated up to 3 times for each attack) for a period of 3 months. The primary effectiveness endpoint (PEE) was mean reduction of headache days compared to baseline. The PEE was compared to the performance goal: a statistically-derived, estimated placebo effect size of -0.6 day reduction of headache days from baseline. In 132 subjects, the mean reduction of headache days from baseline (9.1 days) was 2.8 days (P<0.0001). This result was statistically significant compared to the performance goal. There were no serious AEs. The most frequently reported AEs were light-headedness (4.5%), tingling (3.9%), and tinnitus (3.9%). A total of 9 patients withdrew from the study because of AEs.

Simvastatin plus vitamin D

Simvastatin plus vitamin D is effective for prevention of episodic migraine. In a randomised, double-blind, placebo-controlled trial the combination was well tolerated, and may also provide an economical approach to reduce the increased risk for vascular diseases among migraineurs, the authors concluded [9]. They performed a trial with a 12-week baseline period and 24-week intervention period in 57 adults. Participants were randomly assigned to simvastatin 20 mg tablets twice-daily plus vitamin D3 1,000 IU capsules twice-daily or matching placebo. In the active treatment group, participants experienced a decrease of 9 migraine days, compared to 3 more days of migraine in the placebo group (P<0.001). A total of 9 patients (29%) vs. 1 patient (3%) experienced 50% less migraine days at 24 weeks. AEs were similarly low in both groups.

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Movement Disorders

Interesting findings were presented of studies of advanced and of treatment-resistant Parkinson's disease (PD). Gene therapy for PD is well tolerated and potentially effective. Extended-release carbidopa-levodopa increased the duration of motor symptom improvement in advanced PD. Subcutaneous apomorphine provided significant reduction in OFF time in refractory PD. Reports on the treatment of Huntington disease and tardive dyskinesia have also been included.

Gene therapy for advanced Parkinson's disease

Dose-dependent improvements in functional and quality of life measures were announced from a trial of gene therapy for advanced PD [1]. AAV-hAADC (adeno-associated virus with the inserted human gene for aromatic L-amino acid decarboxylase) was well-tolerated, provided dose-dependent gene expression and potential clinical efficacy.

The phase 1b trial was designed to evaluate the safety of AAV-hAADC. A total of 10 patients with advanced PD received bilateral infusion of AAV-hAADC vector (0.83 x 1012 vg/ml) co-infused with gadoteridol. Of the total, 5 subjects in cohort 1 received up to 450 µL/putamen and 5 subjects in cohort 2 received up to 900 µL/putamen. At baseline and after 6 months gene expression was assessed. Only 21% of the putamen was covered by vector in cohort 1, and 34% in cohort 2. Treatment was well tolerated with no vector-related serious AEs. At the time of reporting, 5 and 3 subjects had completed the 12-month evaluation in cohort 1 and 2, respectively. At 12 months, mean off-medication UPDRS motor scores fell by 16.4 and 14.3 points in cohort 1 and 2. On-medication scores increased 1.8 points in cohort 1, but fell 9.3 in cohort 2. Due to improved motor function, daily levodopa equivalents were reduced by 10% in cohort 1 and 35% in cohort 2. On-time without troublesome dyskinesia's increased by 1.6 and 4.1 hours in cohort 1 and 2.

Table 2 VY-AADC01 phase 1b interim results on UPDRS-II, -IV, and PDQ-39 scores

Functional/Quality of Life Measure	Baseline score	Results at 12-months[1]
UPDRS-II (off-medication)	Cohort 1 (13.6) Cohort 2 (16.7)	Cohort 1 (0.2-point worsening, SD 3.7) vs. Cohort 2 (4.0-point improvement, SD 1.0)
UPDRS-IV total score	Cohort 1 (7.8) Cohort 2 (8.7)	Cohort 1 (1.2-point improvement, SD 1.9) vs. Cohort 2 (2.7-point improvement, SD 3.1)
PDQ-39 total score	Cohort 1 (18.2) Cohort 2 (12.3)	Cohort 1 (1.9-point improvement, SD 5.6) vs. Cohort 2 (9.2-point improvement, SD 5.5)

1) Cohort1 baseline and 12-month data from 5/5 patients. Cohort 2 baseline and 12-month data from 3/5 patients. 2/5 patients in Cohort 2 have not reached 12-month follow-up period at the time of the analysis.

IPX203 in advanced Parkinson's disease

Another important finding with regard to advanced PD was the results of an extended-release formulation of carbidopa-levodopa, named IPX203 [2]. Compared to immediate-release carbidopa-levodopa (CD-LD) and to extended-release CD-LD (IPX066, RYTARY®), IPX203 significantly increased the duration of motor symptom improvement, without increasing troublesome dyskinesia which often accompanies treatment with immediate-release CD-LD in advanced PD. Of 26 patients in this crossover study, 25 completed all 3 periods. The proportion of patients turning ON by hour 1 was similar between IR, ER, and IPX203. IPX203 decreased mean OFF-time (4.5 hr) vs. IR (7.2 hr, $P<0.0001$) and vs. ER (5.4 hr, $P<0.05$). IPX203 correspondingly increased ON-time vs. both comparators without significantly increasing troublesome dyskinesia. IPX203 increased the duration of both a 4-point improvement and a 13-point improvement in the Unified PD Rating Scale (UPDRS) Part 3. AEs were reported by 28.0% (immediate-release), 8.0% (extended-release), and 19.2% (IPX203) of patients, most notably nausea, dizziness, and hypertension. No serious AEs were reported.

Final results of the GLORIA trial showed that levodopa-carbidopa intestinal gel led to significant and sustained reductions in dyskinesia over 24 months in advanced PD patients with ≥4 h/day dyskinesia at baseline [3]. Of the 375 patients enrolled in the registry, 258 (69%) patients completed the 24 months follow-up. Patients were allocated into subgroups based on baseline h/day dyskinesia: Non-Dyskinesia (NDYS) <4h (n=118) and Dyskinesia (DYS) ≥4h (n=139). Both groups had significant improvements in OFF time. Tolerability of the levodopa-carbidopa intestinal gel was comparable between the subgroups.

Apomorphine in refractory Parkinson's disease

Level 1 evidence was presented that apomorphine subcutaneous infusion (APO) provides a significant and clinically meaningful reduction in OFF-time, without increasing dyskinesia's, in PD patients with motor fluctuations that are not well controlled on optimised medical treatment [4].

This was tested in the phase 3 trial TOLEDO, the first prospective, randomised, multicentre, double-blind study of the efficacy of APO vs. placebo. A total of 106 patients from 23 centres in 7 countries were randomised to receive APO during waking time (16±2 hours; ≤8 mg/hour), or placebo. APO provided significantly greater reduction in OFF time between baseline and week 12 than placebo (-0.58 vs. -2.47 hours, respectively; P=0.0025). The reduction in OFF-time with APO was already observed in the first week of treatment and sustained over 12 weeks, and was associated with a significantly greater increase in ON-time without troublesome dyskinesia. The beneficial effects of APO were reflected in higher scores for Patient Global Impression of Change (PGIC) vs. placebo at week 12 (P<0.001). APO was generally well tolerated; no unexpected AEs were observed. Of note: apomorphine was first produced in 1865.

Cognition and Parkinsonism

Worse cognitive functioning is associated with an increased risk of incident Parkinsonism [5]. Importantly, this association is not driven by diagnostic delay, and extends beyond patients with secondary Parkinsonism.

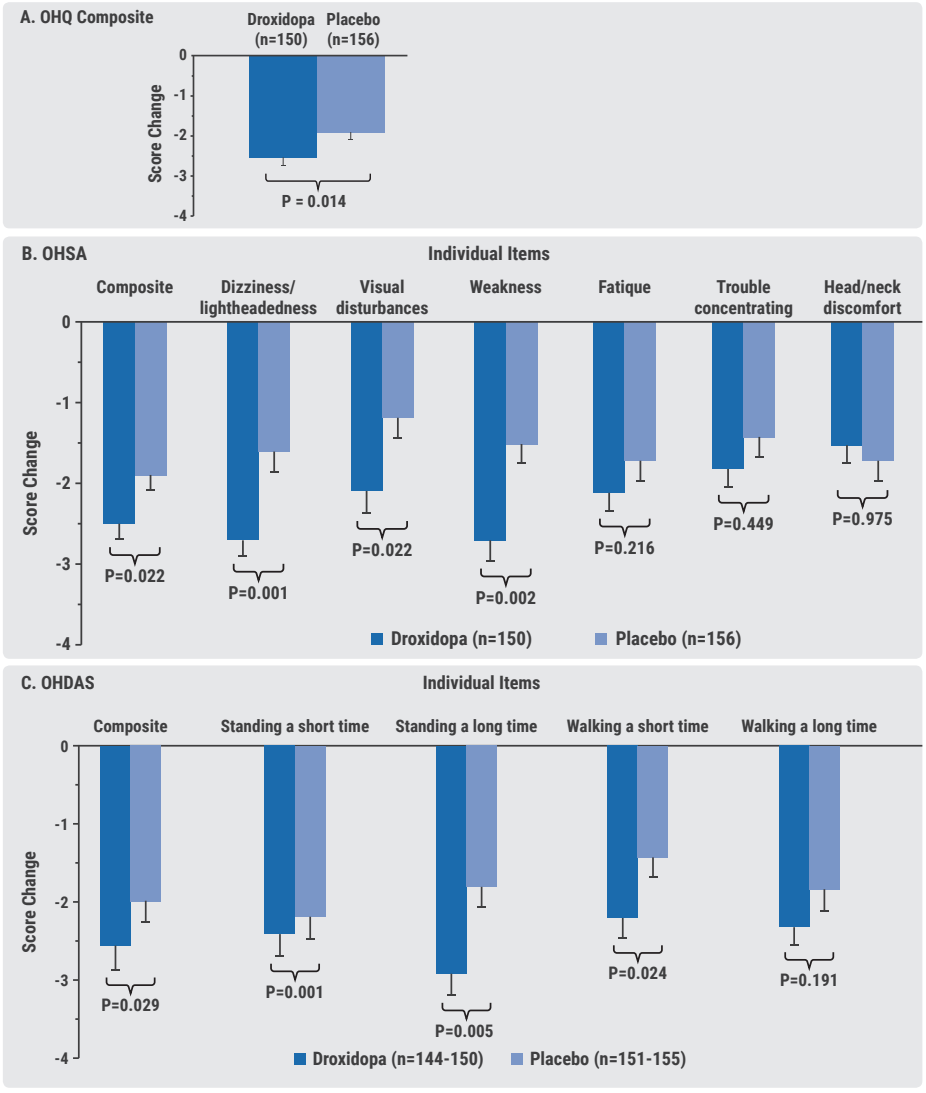
In 8,324 participants of the Rotterdam Study who were free of Parkinsonism and dementia, cognitive function was assessed between 2002 and 2008. The researchers employed four tests: Stroop Colour Word Test, Letter-Digit Subtraction-Test, Verbal Fluency, and Word Learning Test. During a median follow-up of 8.2 years, 92 participants were diagnosed with incident Parkinsonism, 53 (58%) of whom with PD. 31 were also diagnosed with incident dementia; 13 before, 18 after Parkinsonism onset. Lower global cognition was associated with a higher risk of incident Parkinsonism (HR per -1 standard deviation =1.94). The association remained robust beyond the first five years (HR=1.66) and after exclusion of patients with subtle motor features (1.75), secondary Parkinsonism (1.63), or incident dementia (1.89). Letter-Digit Subtraction-Test (HR=1.68), verbal fluency (1.63), and inverted Stroop (1.64) scores were each strongly associated with incident Parkinsonism.

Parkinson's disease and orthostatic hypotension

A pooled subgroup analysis supports the clinical benefit and tolerability of droxidopa for the treatment of PD patients with neurogenic orthostatic hypotension (nOH) [6]. Significant improvements in standing systolic BP, nOH symptoms, and their impact on activities of daily living were demonstrated, despite prominent placebo-effects on symptom measures.

The researches performed a post-hoc analysis of the efficacy of droxidopa (100–600 mg, 3 dd) in the subgroup of patients with nOH and PD, using integrated data from 3 RCTs. Key efficacy outcomes included standing BP measurements and Orthostatic Hypotension Questionnaire (OHQ) scores, which assess nOH symptoms (Orthostatic Hypotension Symptom Assessment: OHSA), and their impact on daily activities (Orthostatic Hypotension Daily Activity Scale: OHDAS). 307 patients with PD were randomised to droxidopa or placebo. Significant

Figure 2 Mean changes from baseline to end of study/week 1 in OHQ, OHSA, and OHAS scores



increases in standing mean systolic/diastolic BP were found for droxidopa vs. placebo (P=0.003/0.002). Droxidopa treatment was associated with significant improvements in OHQ, OHSA, and OHDAS composite scores (P=0.014, 0.022, and 0.029, respectively; Figure 2). It was also associated with statistically significant improvements in 3 of 6 OHSA individual items and 2 of 4 OHDAS individual items, including the cardinal symptoms of nOH: dizziness/light-headedness (P=0.001). Droxidopa was generally well-tolerated; common AEs included headache, dizziness, nausea, and fatigue.

Huntington disease and tardive dyskinesia

- Pridopidine did not improve motor function at week 26 in Huntington Disease (HD) compared to placebo in the phase 2 trial Pride-HD [7]. Pridopidine may confer delay in functional decline as measured by total functional capacity.
- A descriptive study provided insights into the real-world use of tetrabenazine in patients with HD chorea [8]. A considerable percentage of patients discontinued tetrabenazine therapy, and lower-than-expected mean daily doses were achieved. Known tolerability concerns may have limited its use.
- Pridopidine-treated HD patients experience slower total functional capacity decline compared with matched placebo controls from other studies [9]. This result of an exploratory analysis is consistent with data from the recently completed Pride-HD study.
- Regardless of dopamine-receptor antagonist use, deutetrabenazine provided clinically significant reductions in abnormal involuntary movements of tardive dyskinesia (TD), and showed a favourable safety/tolerability profile. In the phase 3 AIM-TD trial, greater reductions were observed in patients not taking dopamine-receptor antagonists, possibly due to masking of TD symptoms by dopamine-receptor antagonists [10].
- Valbenazine may be a promising agent in the long-term treatment of TD [11,12]. TD improved in subjects receiving valbenazine for 48 weeks, reappearing after medication was withdrawn. Valbenazine was well tolerated; TEAEs observed with long-term exposure were consistent with those reported in the DBPC trials. Long-term valbenazine did not have any notable effects on cardiac or hepatic function, and psychiatric status remained stable.

Remote assessments in a clinical trial

Many reports involved some form of telehealh. One study directly compared remote assessments to in-person assessments in a clinical PD trial, in order to evaluate the feasibility, reliability and value of conducting such trials virtually [13]. The researchers presented interim results of an add-on study of 40 PD patients so far enrolled in the STEADY-PD 3 trial. They complete virtual research visits using tablets. Virtual visits occur within 2 weeks of in-person trial visits. All motor and symptom assessments performed during in-person visits are performed remotely. So far, 14 participants had completed their first visit. All assessments had been successfully completed remotely as per protocol. Provider and participant opinions of the remote assessments were positive. Web-based clinical trial assessments (virtual research visits) may limit costs by reducing infrastructure costs, improving inter-rater reliability, and improving recruitment and retention.

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Multiple Sclerosis

As usual, an impressive amount of studies of MS treatments and other aspects of this disease were presented at the AAN meeting. Truly a first were the results of autologous Epstein–Barr virus (EBV) specific T-cell therapy in patients with progressive MS. Other results shed "some light of hope", as one presenter put it, for patients with SPMS, most notably results of opicinumab and siponimod.

Autologous EBV-specific T-cells in progressive multiple sclerosis

A report of clinical improvement in a prospective trial of autologous EBV specific T cells to treat progressive MS patients (Expended disability status scale (EDSS) 5.0–8.0) [1]. Thus far, 4 SPMS patients and 1 PPMS patient have been treated. Each patient receives their own T-cells stimulated ex vivo to enhance reactivity to EBV nuclear antigen-1, latent membrane protein-1 (LMP1) and LMP2A, and is followed through 26 weeks.

No significant AEs were observed. A total of 3 patients experienced symptomatic and objective clinical improvement, which was most marked in the 2 patients receiving T cells with the highest EBV reactivity. Striking improvement occurred in 1 SPMS patient, with normalization of lower extremity tone and plantar responses for the first time in 16 years, increased walking distance with walker from 100 m in the last 5 years to 1200 m, marked reduction in fatigue, increased manual dexterity, and improvements in lower extremity power, reflexes and sensation. A second SPMS patient experienced reduced fatigue, increased productivity and improved balance. The third responder (PPMS) had improved colour vision, visual acuity and manual dexterity, and reduced fatigue, lower extremity spasms and urinary urgency.

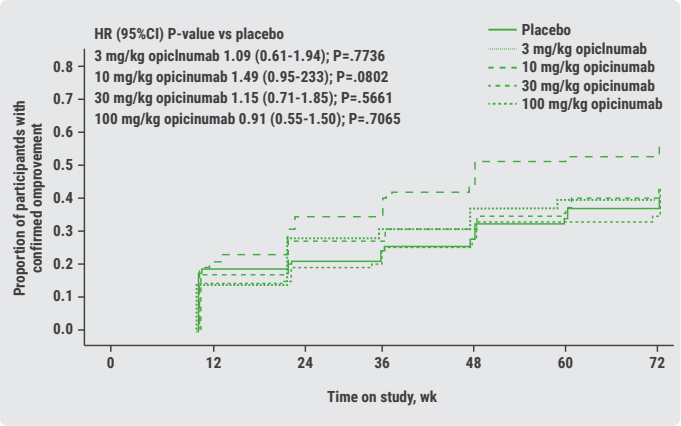
Candidate reparative therapy

Also much anticipated were the results of the double-blind SYNERGY study, evaluating the efficacy of opicinumab in active RRMS or SPMS, used concurrently with intramuscular (IM) IFN beta-1a [2]. Opicinumab blocks LINGO-1, a negative regulator of myelination and axonal regeneration. The primary endpoint, a ≥3 month confirmed improvement of neurophysical and/or cognitive function over 72 weeks, was not met (P=0.8931). However, there was an increased percentage of improvement responders in opicinumab-treated arms vs. placebo at 10 and 30 mg/kg, with an unexpected inverted U-shaped dose-response.

The 418 participants were randomised to 4 opicinumab (3, 10, 30 or 100 mg/kg) or placebo every 4 weeks for 19 doses. They also received IM IFN beta-1a 30 mcg once weekly. A total of 334 patients completed the study. The estimated percentage of improvement responders was 51.6% for placebo, 51.1% for 3 mg/kg opicinumab (OR 0.98), 65.6% for 10 mg/kg (OR 1.79), 68.8% for 30 mg/kg (OR 2.06) and 41.2% for 100 mg/kg (OR 0.66). Additional pre-specified analyses revealed that 10 mg/kg had the most consistent treatment response [3]. These additional analyses included confirmed improvement and time to confirmed improvement on A) a multicomponent endpoint comprising EDSS, Timed-25 Foot Walk Test (T25FW), and 9-hole Peg Test (9HPT); and B) ≥2 of these components (Figure 3). Opicinumab was generally well tolerated in RMS, with better tolerability at lower dose [4].

Safety and efficacy of opicinumab has also been evaluated in acute optic neuritis [5]. Remyelination did not differ significantly with placebo in the intention-to-treat population at week 24. However, results do suggest that enhancing remyelination with opicinumab is possible.

Figure 3 Proportion of participants with improvement on the alternative multicomponent endpoint (EDSS, T25FW, and 9HPT)



Robust effects siponimod in secondary progressive multiple sclerosis

In the placebo controlled phase 3 study EXPAND, siponimod showed a robust positive effect on disability progression and other relevant outcomes in SPMS [6], "shedding some light of hope", as Prof Dr L. Kappos from Geneva said. Siponimod reduced the risk of 3-month confirmed disability progression (CDP) by 21% vs placebo (P=0.013). Point estimates in favour of siponimod were consistently observed across predefined subgroups. The risk reduction observed for T25FW was 6.2%, which was not statistically significant (P=0.440). "This is less a problem of the drug than of the test", Kappos commented. Siponimod reduced the risk of 6-month CDP by 26% (P=0.006), annualised relapse rate by 55.5% (P<0.0001), T1 Gd+ lesion number by 86.6% (P<0.0001), and new T2 lesion number by 81% (P<0.0001). Kappos: "Siponimod is certainly an option in SPMS".

The safety results of siponimod were presented separately. They appear to be in line with other S1P receptor modulators [7]. At least 1 TEAE was reported for 88.7% and 81.5% of siponimod and placebo patients, respectively. Serious TEAEs were reported in 17.9% and 15.2%.

Natalizumab in secondary progressive multiple sclerosis

The ASCEND open-label extension showed that full benefits of natalizumab on disability progression, particularly lower-limb function, in advanced SPMS patients may not be evident until after longer treatment duration [8]. During the study's 2-year randomised treatment period, natalizumab did not delay disability progression in SPMS patients, assessed by the primary composite endpoint (EDSS, T25FW), and 9-Hole Peg Test (9HPT), but it did slow progression on the 9HPT (upper-limb) component. In the ASCEND open-label extension, clinically meaningful benefits on disability progression in advanced SPMS patients after 3 years were reported on the primary composite endpoint. The largest treatment benefit was seen on preserving 9HPT, but preservation of ambulatory function (T25FW and EDSS) was also observed.

Another study showed that patients initiating natalizumab soon after symptom onset (≤1 year) had a higher probability of on-treatment disability improvement than patients initiating later [9]. Thus, early MS disability may reflect inflammation that can be mitigated by timely natalizumab treatment, whereas later disability may be more resistant to recovery.

DMF option for paediatric patients?

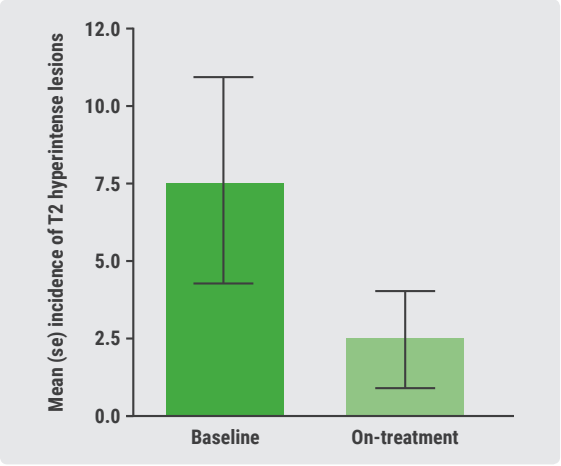
Delayed-release DMF may prove to be a treatment option for paediatric RRMS patients. In the FOCUS trial, the efficacy, safety, and pharmacokinetics of DMF in paediatric MS patients were consistent with those observed in adult patients [10]. It is the first clinical trial to examine the neuroradiological efficacy of any disease modifying therapy in children. From 12 sites, 22 patients (10–17 years) were enrolled. The mean change in the number of new/newly enlarging T2 hyperintense lesions was -7.9; the median was -2.0 (P=0.009). The most common AEs were gastrointestinal events (55%), flushing (45%), and MS relapse (32%). Lymphopenia, alanine aminotransferase elevation, and aspartate aminotransferase elevation occurred in 23%, 15%, and 10% of patients, respectively.

In a post-hoc subgroup analysis of the open-label RESPOND study, DMF 240 mg twice daily was associated with a lower annualised relapse rate in 231 adult relapsing MS (RMS) patients, including patients with early MS, after suboptimal response to glatiramer acetate [11].

Alemtuzumab – CARE-MS 1 and 2

A very low proportion of alemtuzumab treated patients from the CARE-MS 1 and CARE-MS 2 studies progressed to SPMS through 6 years [12]. EDSS scores were stable/improved with alemtuzumab over 6 years in >75% of patients with active RRMS who were treatment-naive (CARE-MS 1) or who had relapsed to prior therapy (CARE-MS 2). 325/376 (86%) and 344/435 (79%) of alemtuzumab-treated patients, respectively, remained on study through year 6. The majority received no additional treatment in the extension. Among

Figure 4 Mean incidence of T2 hyperintense lesions during the baseline period vs. the on-treatment period



alemtuzumab-treated CARE-MS 1 or 2 patients, the SPMS definition was met by only 4 (1.1%) and 16 (3.7%) patients, respectively. In an MS-Base patient cohort of MS patients (n=17,356), 18% of all patients converted to SPMS.

There were other findings from the extensions of CARE-MS 1 and 2. Efficacy of alemtuzumab on Magnetic Resonance Imaging (MRI) disease activity was also durable over 6 years without continuous treatment [13]. In patients with highly active RRMS, alemtuzumab improved MRI outcomes through 6 years [14]. In each extension year, most patients were free of MRI disease activity: year 3: 65%, year 4: 67%, year 5: 70%, year 6: 65%. Following a switch from SC IFNB-1a, alemtuzumab reduces the rate of brain volume loss, and decreased MRI disease activity over 4 years [15,16].

Ocrelizumab

A number of studies presented of ocrelizumab highlighted both the rapidity of onset of action, and the efficacy in the long term. Ocrelizumab demonstrated beneficial effects on brain MRI activity in RRMS relative to placebo and IFNβ-1a as early as week 4, supporting a rapid suppressing of brain lesions [17]. In the first 24 weeks, 218 patients received placebo, ocrelizumab 600 mg, ocrelizumab 2000 mg, or IM IFNβ-1a 30 µg. Ocrelizumab reduced the total number of new T1 Gd+ lesions at week 4 by 62% vs. placebo (P=0.0423), and the number of new T1 Gd+ lesions between weeks 4 and 8 by 97% vs. IFNβ-1a (P<0.0001). The mean total number of new T2 lesions appearing between weeks 4 and 8 was 0 for ocrelizumab vs. 0.717 for placebo and 0.609 for IFNβ-1a. Ocrelizumab reduced the total number of newly enlarging T2 lesions appearing between weeks 4 and 8 by 93% vs. placebo (P=0.0030) and 90% vs. IFNβ-1a (P=0.0162).

In a pooled analysis of the identical OPERA 1 and OPERA 2 studies, ocrelizumab reduced relapse occurrence vs. IFNβ-1a throughout 96 weeks, with significant reductions already occurring in week 8 [18]. Ocrelizumab reduced annualised relapse rate from baseline to week 96 by 46.5% vs. the active comparator (HR 0.156 vs. 0.291; P<0.0001). Patients who originally received ocrelizumab in the OPERA studies continued to have favourable annualised relapse rate outcomes in the OLE [19]. Switchers to ocrelizumab rapidly experienced annualised relapse rate consistent with those of patients who received continuous ocrelizumab.

Efficacy and safety of cladribine tablets

An extension to the CLARITY study (CLARITY EXT) demonstrates durable clinical benefits from cladribine: patients who received cladribine in CLARITY and placebo in CLARITY EXT maintained low relapse rates throughout [20]. Continuing treatment with cladribine in CLARITY EXT did not bring additional benefits. For patients who received placebo in CLARITY, switching to cladribine in the extension significantly reduced annualised relapse rate (0.26 vs. 0.10, P<0.0001) and increased the chance to become relapse-free.

The AE profile for cladribine CT 3.5 mg/kg as monotherapy has now been well-characterised in a pooled population of patients with early MS or active RMS [21]. The cohort was comprised of 923 patients; 641 patients in this cohort received placebo. AE per 100PY for lymphopenia were 7.94 and 1.06, respectively; this was expected from cladribine tablets' mode of action. Herpes zoster was reported more frequently in patients experiencing grade 3 or 4 lymphopenia. No clustering of types of malignancy, and no malignancies commonly associated with immunosuppression were observed.

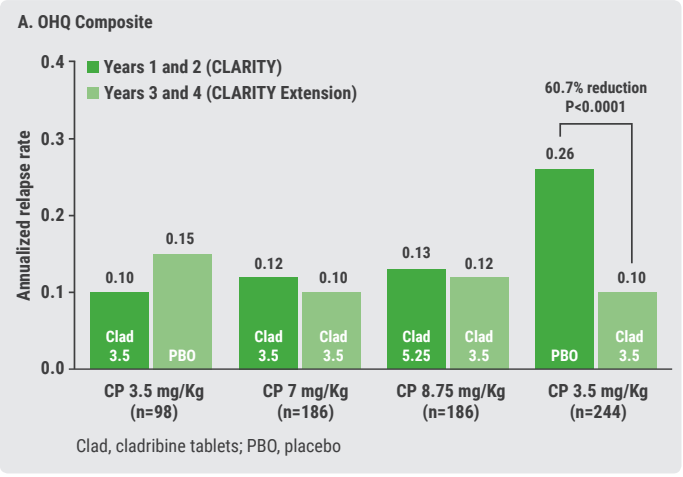
Subgroups of RMS patients with high disease activity in the CLARITY study, showed clinical and MRI responses to cladribine that were at least comparable with, and generally even better than the outcomes in the overall study population [22].

Daclizumab: clinical and magnetic resonance imaging outcomes

Benefits on brain MRI lesion activity observed with daclizumab vs. IM IFNbeta-1a in the DECIDE study were maintained with prolonged treatment in the ongoing, open-label EXTEND study [23]. In an interim-analysis of EXTEND, additional benefits on brain MRI lesion activity were observed in patients who had switched from IM IFN beta-1a to daclizumab.

In a mixed treatment comparison, daclizumab showed improvement in clinical outcomes vs other disease modifying therapies and placebo in RRMS patients [24]. In 30 relevant studies, daclizumab reduced annualised relapse rate relative

Figure 5 Annualised relapse rate by treatment group for CLARITY and CLARITY extension [21]



to 10 of 12 comparators including placebo, with 6 of 10 comparisons showing statistically significant differences, including vs placebo. Furthermore, daclizumab reduced risk of disability progression confirmed at 12 weeks (CDP12W) relative to 8 of 11 comparators including placebo, and risk of CDP at 24 weeks relative to 5 of 6 comparators, including placebo.

Gene expression to classify multiple sclerosis

Use of gene expression data obtained from whole blood and analysed with machine learning methods delivers a highly accurate, actionable tool for providers who suspect MS, researchers reported [25]. Messenger RNA (mRNA) and long, non-coding RNA (lncRNA) expression data were used to accurately classify MS. lncRNAs are a relatively new class of RNA that play pivotal roles in the regulation of biological processes including innate and adaptive immune responses. Compared to mRNAs, lncRNAs exhibited greater discriminatory power and confidence of machine learning predictions, with sensitivity and specificity exceeding 90% across case/control comparisons. Differences in expression of annotated lncRNAs ranged in magnitude from 4-fold to 32-fold across the study cohorts, while differences in expression of mRNAs were typically less than 4-fold.

Other trials in short

- Final results from the BETAPAEDIC study suggest that IFNbeta-1b is an effective treatment with a favourable tolerability profile for paediatric RRMS patients [26]. Patients were 68 treatment-naïve children of 12–16 years. The most frequent drug-related AEs were flu-like symptoms (46.3%), headache (19.4%), injection site reactions (16.4%), and abnormal liver function tests (11.9%).
- Radiological evidence suggests a continuous long-term effect of fingolimod on disease activity in patients with RRMS in the LONGTERMS study [27]. In the full analysis set (n=3127), annualised rate of new or newly enlarging T2 lesions gradually decreased from 1.362 at month 12 to 1.011 at year 3, 0.915 at year 5, and 0.801 at year 8. Of 924 evaluable patients, 48.3% remained free from Gd+ T1 lesions throughout the study.
- In the phase 4 Teri-PRO study, disability remained stable in patients treated with teriflunomide regardless of prior treatment, and treated relapse rate was low [28]. The safety profile was consistent with that observed in the clinical development program. And a subgroup analysis of data from the SIENA trial revealed teriflunomide reduces brain volume loss in previously treated patients [29].
- In a retrospective study of the comparative effectiveness of DMF, fingolimod and teriflunomide, there was no difference in relapse rate between DMF and fingolimod [30]. Teriflunomide was associated with a significantly higher relapse rate relative to DMF. Results were consistent among newly-treated and switching patient subgroups.

Impact of MS on daily activities

The impact of MS on individuals' daily activities, emotional well-being, relationships, and employment was assessed using vs MS [31]. This 20-minute electronic survey was completed by 1075 participants with MS and 580 care partners from 7 countries. Participants reported their daily activities were limited by fatigue (76%; 18% severely), bladder/urinary problems associated with MS (45%; 8%), depression or anxiety (48%; 7%), trouble concentrating (52%; 8%), and ability to understand or learn new things (41%; 5%). 71% of participants agreed that potential disability worsening was their greatest concern; 49% felt their future outlook, and 44% felt their emotional well-being, had worsened; 26% feared their partner may leave them; and 44% felt less sexually attractive. A total of 64% of participants thought their MS affected their ability to keep their job. These data highlight the importance of addressing disease burden in daily practice.

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Neuromuscular Disorders

A remarkable number of trials of new experimental treatments in the realm of neuromuscular disorders were presented, often with very encouraging results. What stood out during this AAN meeting were the results of 2 new treatments for patients with spinal muscular atrophy (SMA): AVXS-101 gene therapy, and intrathecal nusinersen. A video of a child that walked after AVXS-101-therapy, shown in a plenary session, was greeted with spontaneous applause.

Impactful gene therapy in spinal muscular atrophy

In the first-ever gene therapy trial in SMA Type 1 (SMA1), a single intravenous administration of AVXS-101 appeared to demonstrate a positive impact on the survival of both dosing cohorts [1]. Thus far, it has had a dramatic, sustained impact on motor function in the larger of 2 cohorts, cohort-2: 11/12 patients achieved CHOP-INTEND scores and motor milestones rarely or never seen in this population.

The 15 enrolled patients received AVXS-101 at 6.7e13 vg/kg (cohort-1, n=3) or 2.0e14vg/kg (cohort-2, n=12), carried by a harmless virus to cross the blood-brain barrier. The primary objective is safety; secondary objectives include avoidance of death/permanent ventilation, and the ability to sit unassisted. AVXS-101 appeared safe and to improve survival. All patients were alive and only 1 patient, from cohort 1, reached the pulmonary endpoint at 28.8 months of age. All patients reaching 13.6 months did so free of permanent ventilation. Patients in cohort-2 demonstrated improvements in motor function: 11/12 had CHOP-INTEND scores >40 points, 11/12 had head control and could sit unassisted, and 8/12 were able to speak. Two patients could crawl, stand and walk independently. According to Dr. J.R. Mendell from Columbus, Ohio, the overall safety was "impeccable". He found it very gratifying to work on this "hugely successful" trial.

Nusinersen efficacious in spinal muscular atrophy

Also presented were results of two phase 3 trials of nusinersen in infants with SMA: the sham-procedure controlled ENDEAR and CHERISH studies [2,3]. Nusinersen is an investigational antisense oligonucleotide.

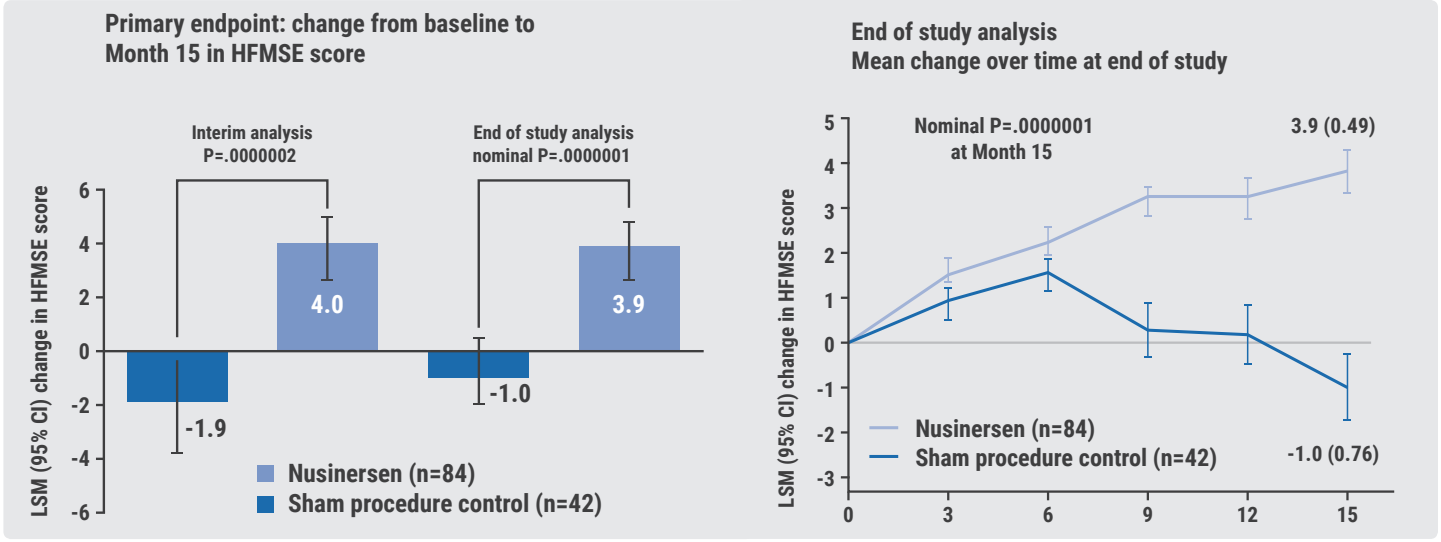
In ENDEAR, nusinersen (12 mg scaled equivalent dose) met the primary endpoint of the interim analysis in infants (≤7 months at screening) with SMA type 1. Statistically and clinically significant improvements were observed in motor milestones: ≥2 point increase (or maximal score) in ability to kick or ≥1 point increase in head control, rolling, sitting, crawling, standing or walking, and improvement in more categories of motor milestones than worsening.

In CHERISH, significant improvements in motor function were observed as well. At the time of the interim-analysis, 126 children with later-onset SMA (>6 months) aged 2-12 years had been enrolled. They received 4 doses of intrathecal nusinersen (12 mg non-scaled) or sham procedure over 15 months. The primary endpoint was change in the Hammersmith Functional Motor Scale–Expanded (HFMSE) score. The difference with placebo was highly clinically and statistically significant: least square mean treatment difference 5.9 points (P=0.0000002). HFMSE scores increased ≥3 points in 57.3% of nusinersen-treated vs 20.5% of sham-treated children; 17.1% vs 10.5% achieved new world health organisation motor milestones, respectively. In both studies, nusinersen was generally well tolerated and demonstrated a favourable safety profile. SMA patients from both ENDEAR and CHERISH are transitioned to the SHINE open-label extension study.

Eteplirsen for Duchenne muscular dystrophy

Eteplirsen is the first exon skipping therapy approved for the treatment of Duchenne muscular dystrophy (DMD) amenable to exon 51 skipping. It was shown to boost dystrophin production, and improve functional ability. Dr. J.R. Mendell presented an analysis of 6-Minute Walk Test (6MWT) performance over 4 years, comparing boys treated with 30 or 50 mg/kg/wk eteplirsen 4 (n=12) with a group of comparable, untreated external controls (n=13) as defined by age, corticosteroid use, and genotype [4]. After 1 year, there was no clear benefit, after 2 years a highly significant benefit of 75 m on 6MWT was seen, after 4 years this benefit was 162 m vs external controls (P=0.0005). Sensitivity analyses of 6MWT with covariates resulted in differences >150 meters between the groups (P<0.01). In addition, the risk of loss of ambulation was reduced (P=0.011). Only 2 of 12 patients (17%) lost ambulation during the study, while 46% of historical controls lost ambulation at 3 years and 85% lost ambulation by 4 years. The treatment was very well tolerated; most treatment-related AEs were related to the infusions or biopsy. As Mendell concluded: "We're making great progress".

Figure 6 Mean change from baseline in HFMSE score at: (A) prespecified interim analysis (primary endpoint); (B) end of study; and (C) over time at end of study



HFMSE = Hammersmith Functional Motor Scale Expanded: LSM = least-squares mean: SMA = spinal muscular atrophy. Descriptions of statistical analyses in notes sections of slide. 'From baseline to Month 15. Interim analysis: observed: sham procedure control, n=19; nusinersen, n=35; imputed: sham procedure control. n=23; nusinersen n=49. End of study analysis: observed: sham procedure control, n=34; nusinersen, n=66; imputed: sham procedure control n=8, nusinersen n=18.

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Eculizumab in refractory generalised myasthenia gravis

Three times as many patients with refractory generalised myasthenia gravis treated with eculizumab experienced improvements in muscle strength that benefited daily activities, than in the placebo group by week 26 in the phase 3 REGAIN study [5]. Improvement was observed early and continued to expand.

Refractory generalised myasthenia gravis patients continued to receive a stable dose of immunosuppressive therapy and were randomised to receive eculizumab (n=62) or placebo (n=63). A clinically meaningful response was defined as: A) reduction of ≥3 points from baseline in the Myasthenia Gravis Activities of Daily Living total score, and B) a reduction of ≥5 points from baseline in the Quantitative Myasthenia Gravis total score, both with no rescue therapy. A total of 40% of patients in the eculizumab group vs 13% in the placebo group achieved clinically meaningful responses at week 26 on both scales (nominal P=0.0004). The benefit of eculizumab was apparent within 2 weeks. Improvement with eculizumab was generally observed by week 8 (36% vs. 14%, nominal P=0.0060).

Efficacy of IgPro20 for chronic inflammatory demyelinating polyneuropathy

For the first time, subcutaneous immunoglobulin (SCIg) – as an alternative to intravenous Ig – has been evaluated in a large-scale clinical trial in chronic inflammatory demyelinating polyneuropathy (CIDP). In a double-blind RCT, SCIg IgPro20 (0.2 and 0.4 g/kg weekly) was efficacious and safe as maintenance treatment [6]. In 172 subjects, both high- and low-dose SCIg (0.4 and 0.2 g/kg/wk) were superior to placebo, with the high dose potentially showing better efficacy. The primary outcome was the percentage of subjects who had a CIDP relapse (1-point deterioration on adjusted INCAT disability score) or were withdrawn for any other reason during the 24-week SCIg-treatment period. This outcome occurred in 33% of high-dose SCIg, 39% of low-dose SCIg, and 63% of placebo subjects (P<0.001); CIDP relapse occurred in 19%, 33% and 56% (P<0.001), respectively. High-dose SCIg prevented the decline in Rasch-built Overall Disability Scale (R-ODS) score seen with low-dose SCIg and placebo (P<0.001). Causally related adverse events occurred in 47 (27%) subjects (30% low dose, 35% high dose, and 18% placebo).

New treatment for LGMD2B and facioscapulohumeral muscular dystrophy

In a pilot, open-label study, ATYR1940 administered up to 3 mg/kg biw was safe and well-tolerated in patients with Limb Girdle Muscular Dystrophy Type 2B (LGMD2B) and Facioscapulohumeral Muscular Dystrophy (FSHD) [7]. ATYR1940 is a physiocrine based protein that is substantially identical to human histidyl-tRNA synthetase. Eighteen patients were assigned to group A or B for one week of placebo, then 12 weeks of ATYR1940. In group A, 4 FSHD patients received ATYR1940 titrated to 1.0 mg/kg biw; in group B, 10 LGMD2B and 4 FSHD patients received ATYR1940 titrated to 3.0 mg/kg biw. Mean change from baseline to week 14 for manual muscle testing was -7.1% for FSHD group A, 0% for FSHD group B, and +6.2% for LGMD2B group B. No consistent changes over time were observed in Individualized Neuromuscular Quality of Life (INQoL) scores, circulating biomarkers or MRI. ATYR1940 was well-tolerated at all doses tested. Adverse events were mild or moderate in intensity.

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