In the news

LATE-BREAKING NEWS AT ECTRIMS 2018

In October 2018, over 9,400 delegates gathered in Berlin for the 34th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) — the world's largest conference on multiple sclerosis (MS). Recurring themes during the congress included the application of real-world data to treatment decision-making, the use of neurofilament light chain as a biomarker for neurodegeneration, and the ongoing challenge of treating progressive forms of MS.

The Late-Breaking News session featured a number of notable 'firsts', including the first demonstration of a reduction in MS disease activity by a Bruton's tyrosine kinase (BTK) inhibitor, the first phase III trial in patients with neuromyelitis optica spectrum disorder (NMOSD), and the first multi-arm trial in secondary progressive MS (SPMS).

BTK inhibitors suppress the activation of B cells and macrophages, and their therapeutic potential is currently being explored in a range of autoimmune disorders. At ECTRIMS 2018, Xavier Montalban presented data from a phase II trial of the BTK inhibitor evobrutinib in patients with relapsing–remitting MS. Compared with placebo, oral evobrutinib treatment at a dose of 75 mg, administered once or twice daily, was associated with reductions in the accrual of gadolinium-enhancing lesions in the brain and in the annualized relapse rate. The investigators concluded that the drug warrants further evaluation in larger trials.

Takashi Namamura reported on the SAkuraSky study, a phase III trial of the anti-IL-6 receptor monoclonal antibody satralizumab in patients with NMOSD. In comparison with placebo, the drug reduced the relapse rate by 62% across the entire cohort and by 79% in a subset of patients who were seropositive for anti-aquaporin-4 antibodies. SAkuraSky is the first phase III trial to be conducted in patients with NMOSD, and the results provide validation of the IL-6 receptor as a therapeutic target in this condition.

Jeremy Chataway described an innovative multi-arm trial that was designed to test potential neuroprotective therapies in patients with SPMS. The MS-SMART trial tested three oral drugs — amiloride, fluoxetine and riluzole — against placebo. Each of the four treatment arms consisted of 110 patients with SPMS, and the primary outcome measure was a reduction in brain atrophy. Unfortunately, none of the drugs met this end point; in fact, the patients who received fluoxetine initially showed acceleration of atrophy. Nevertheless, Chataway concluded that the study design lays down a template for future work.

"While these results are disappointing, well-controlled trials such as the MS-SMART trial will help inform new approaches for future studies aimed at treating progressive forms of MS," commented Alan Thompson, Chair of the Scientific Steering Committee of the International Progressive MS Alliance. "Lessons from this study and others will inform the Alliance's research priorities and those of other international research funders such as the UK MS Society and National MS Society."

Heather Wood

PARKINSON DISEASE

White matter pathology predicts cognitive decline in PD

A large burden of white matter hyperintensities (WMHs) in the brain is predictive of accelerated cognitive decline in patients with de novo Parkinson disease (PD), according to a longitudinal study that was recently reported in *NeuroImage: Clinical*.

WMHs are an MRI marker of cerebral small vessel disease and have been linked to Alzheimer disease and age-related cognitive impairment. However, the relationship between white matter pathology and cognitive dysfunction in PD has not been extensively studied to date.

"Of the few studies that have investigated WMHs and cognitive decline in PD, most are cross-sectional, include patients that are on dopaminergic medication, and are typically from cohorts that are at later stages of disease," the authors comment in their paper.

The new study, led by Louis Collins at the Montreal Neurological Institute (QC, Canada), included 365 patients with de novo PD — that is, individuals in the early stages of PD who had not yet commenced dopaminergic medication — and 174 age-matched healthy controls. Both groups were recruited from the Parkinson's Progression Markers Initiative (PPMI) and were cognitively healthy at baseline.

In the patients with PD, but not in the controls, a high WMH load at baseline was associated with increased cognitive decline over a mean follow-up period of 4 years. In addition, during the first year of follow-up, the degree of cortical thinning in the right frontal lobe correlated with the baseline WMH burden in the patients with PD.

"Our findings suggest that WMH burden is an important predictor of

HUNTINGTON DISEASE

Antisense oligonucleotides improve cognitive function in HD model

Antisense oligonucleotides (ASOs) that suppress expression of mutant huntingtin reduce cognitive and behavioural impairments in a mouse model of Huntington disease (HD), new research shows. The findings add to previously observed benefits of ASOs on motor function, and demonstrate that allele-specific suppression is beneficial.

HD is caused by a CAG repeat expansion in *HTT*, the gene that encodes huntingtin. Targeting of *HTT* with ASOs to suppress expression of the protein has shown promise as a therapy for HD in previous work.

"Substantial preclinical data demonstrate the benefit of lowering huntingtin on motor deficits and physical changes in the brain," explains Michael Hayden, senior author of the new study. "However, the psychiatric and cognitive aspects of the disease, which have a greater impact on patient quality of life, have not been explored."

Hayden and colleagues used a humanized mouse model of HD to test the effects of ASOs that specifically target the mutant *HTT* allele. "We chose ASOs to induce gene suppression because they can be delivered to the CNS with no viral or lipid carrier, freely enter neurons, glia and ependymal cells, have a long brain half-life, and have demonstrated CNS tolerability in the human clinic," explains Hayden.

Administration of the ASOs to young, asymptomatic mice prevented the development of cognitive and behavioural impairments. Administration to old mice after symptom onset reversed existing cognitive deficits.

"This study provides the first evidence that cognitive impairment in HD could